Pediatric Surgery International (2023) 39:7
https://doi.org/10.1007/s00383-022-05282-0

REVIEW ARTICLE

# Intravenous acetaminophen for postoperative pain control after open abdominal and thoracic surgery in pediatric patients: a systematic review and meta-analysis

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Accepted: 16 October 2022 / Published online: 28 November 2022


## Abstract

Pediatric opioid exposure increases short- and long-term adverse events (AE). The addition of intravenous acetaminophen (IVA) to pediatric pain regimes to may reduce opioids but is not well studied postoperatively. Our objective was to quantify the impact of IVA on postoperative pain, opioid use, and AEs in pediatric patients after major abdominal and thoracic surgery. Medline, Embase, CINAHL, Web of Science, and Cochrane Library were searched systematically for randomized controlled trials (RCTs) comparing IVA to other modalities. Five RCTs enrolling 443 patients with an average age of 2.12 years (±2.81) were included. Trials comparing IVA with opioids to opioids alone were meta-analyzed. Low to very low-quality evidence demonstrated equivalent pain scores between the groups (−0.23, 95% CI −0.88 to 0.40, *p* 0.47) and a reduction in opioid consumption (−1.95 morphine equivalents/kg/48 h, 95% CI −3.95 to 0.05, *p* 0.06) and minor AEs (relative risk 0.39, 95% CI 0.11 to 1.43, *p* 0.15). We conclude that the addition of IVA to opioid-based regimes in pediatric patients may reduce opioid use and minor AEs without increasing postoperative pain. Given the certainty of evidence, further research featuring patient-important outcomes and prolonged follow-up is necessary to confirm these findings.

**Keywords** Acetaminophen · Paracetamol · Pain · Post-operative · Pediatric

## Abbreviations

| | |
|---|---|
| CDH | Congenital diaphragmatic hernia |
| CHEOPS | Children's Hospital of Eastern Ontario Pain Scale |
| CI | Confidence interval |
| EHBA | Extrahepatic biliary atresia |
| FLACC | Face, Legs, Activity, Cry, Consolability scale |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluations |
| IQR | Interquartile range |
| IV | Intravenous |
| LoS | Length of stay |
| MED | Morphine equivalent dosing |
| MD | Mean difference |
| MeSH | Medical subject headings |
| NIPS | Neonatal infant pain scale |
| NR | Not reported |
| RCT | Randomized controlled trial |
| RoB | Risk of bias |
| SD | Standard deviation |
| SMD | Standard mean difference |
| SoF | Summary of findings |
| TEF | Tracheoesophageal fistula |
| VAS | Visual analogue scale |

**Level of evidence** Level II [1].

**Study registration** PROSPERO: CRD42021274431.

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## Introduction

Managing postoperative pain in pediatric patients presents various challenges for physicians. Patients' limited ability to communicate their symptoms, wide variations in development and physiology, harmful myths regarding infants' perception of pain, and comparatively less research relative

to adults make developing evidence-based multimodal pain strategies difficult in pediatric populations [2–6]. Opioids are associated with an increased risk of long- and short-term adverse events [7, 8]. Acutely, children experience the same physiologic changes as their adult counterparts, such as decreased respiratory drive, delayed intestinal motility, and sedation, leading to an increased length of stay (LoS) [9, 10]. Long-term adverse events are augmented in pediatric patients as their state of rapid neurologic development places them at increased risk for long-term developmental delays when exposed to opioids [11–13]. Managing this pain is essential, as unmanaged pain can lead to adverse events such as impaired ventilation, circulatory changes, intraventricular hemorrhage, and periventricular leukomalacia. However, it must be balanced against the risks opioids pose [11, 14–16]. A multimodal strategy provides the opportunity to balance pain control and medication-related adverse events. Pain after surgery is physiologically unique from other procedures such, as blood draws or nasogastric tube insertion. Further variation in pain is based on the type of surgery with open abdominal and thoracic surgeries resulting in a different physiologic response than other surgical techniques (i.e., laparoscopic, orthopedic, sternotomies), necessitating individual attention [17–19].

Patients may have restrictions in the immediate postoperative period, limiting the drug's route. Patients may not be able to have oral intake, or in the case of rectal and pelvic surgery, they may not be able to take medications rectally, necessitating intravenous (IV) administration. Physiologically, in pediatrics, specifically in neonates, their intestinal tracts and enterohepatic circulatory systems are in varying stages of maturity, with decreased motility, absorption, and circulation; oral and rectal formulations become less predictable when compared to IV [20–23]. IV administration also avoids first-pass metabolism, resulting in up to 50% less accumulation in the liver and decreased production of hepatotoxic metabolites [24]. There is a paucity of literature regarding the efficacy of IV acetaminophen for postoperative pain control in pediatric populations. For non-abdominal and thoracic surgeries (including non-surgical pain), IV acetaminophen effectively reduces pain and opioid-related side effects [25–28]. Evidence exists suggesting IV acetaminophen is safe and is not associated with liver injury [29]. Additionally, there is evidence demonstrating short-term safety in neonates, with ongoing research evaluating long-term effects [30–34].

### Rationale

A meta-analysis has yet to be conducted to evaluate the effect of IV acetaminophen in pediatric populations after major abdominal and thoracic surgery. The unique pediatric physiology and response to open abdominal and thoracic surgery warrant individual attention, as data from adults and minor surgeries are not applicable.

### Objectives

This systematic review aimed to synthesize the available evidence comparing IV acetaminophen to other pain medications in pediatric patients undergoing open abdominal and non-cardiac-thoracic surgery. Specifically, the aim was to compare pain scores, opioid requirements, and adverse events.

## Methods

### Study design

This was a systematic review of IV acetaminophen for postoperative pain control in children undergoing open abdominal and non-cardiac thoracic surgeries. The primary outcome was postoperative pain scores, and the secondary outcome included opioid requirements, analgesic complications, and LoS. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021274431).

### Search strategy

A systematic search of Medline, Embase, CINAHL, Web of Science, and the Cochrane Library for randomized controlled trials (RCT) comparing IV acetaminophen to any other pain medication for pediatric patients after open abdominal and non-cardiac thoracic surgery was conducted. The search strategy was developed with a research librarian. Medical Subject Headings (MeSH) were used where applicable and included derivatives of acetaminophen, paracetamol, tylenol, ofirmev, intravenous, injection, parenteral, pain, postoperative, procedural, and pediatric. A hand search of the reference lists of relevant studies was also conducted. Studies were restricted to those with full texts available in English. A sample search strategy is available in the supplemental files.

### Study selection and data extraction

Studies were selected if they included patients under 18 years of age who underwent open abdominal or non-cardiac thoracic surgery, compared postoperative IV acetaminophen to any other pain medication, and were RCTs. Studies were excluded if they included other types

of surgery and did not provide specific thoracic or abdominal surgery results and if they only evaluated the effect of pre-or intraoperative IV acetaminophen. There were no exclusion criteria based on language, year, or publication status. We elected to only include thoracic and abdominal surgeries as most available literature evaluates more minor procedures most notably tonsillectomies, but also blood draws, and heel lances [24, 35, 36]. Pain following abdominal and thoracic surgeries results in a different physiologic response than other surgical techniques (i.e., laparoscopic, orthopedic, sternotomies), thus, evidence focusing on other surgeries may not be applicable [17–19].

Title and abstract screening were completed independently and in duplicate by at least two reviewers (VA, LP, ZC). Discrepancies were automatically included in the full-text screen and resolved at that time; a third reviewer adjudicated any unresolved discrepancies. This process was done using Covidence systematic review software [37].

Data were extracted by two independent reviewers (VA, LP, ZC). Any discrepancies were resolved by consensus. A third reviewer adjudicated any unresolved discrepancies. Study authors were contacted to obtain missing data.

## Primary outcome

The primary outcome of this systematic review was postoperative pain scores [reported as standard mean differences (SMDs) and back-transformed to a numeric rating scale (NRS)]. This was extracted at 48 h, as this was the only common time period reported. Other time periods are reported narratively.

## Secondary outcomes

Prespecified secondary outcomes include opioid equivalents used and adverse events (urinary retention, ileus, nausea and vomiting, sedation, and adverse drug reactions), LoS, time requiring mechanical ventilation, and time to first enteral feed. Opioid equivalents (reported as morphine equivalent doses/kg/48 h) were extracted at 48 h as this was the only common time period reported; other time periods are reported narratively. Adverse events were extracted up to 72 h (the longest follow-up period reported). Outcomes not able to be meta-analyzed are reported narratively.

## Demographics

Reviewers also extracted study characteristics (year and country of study) and participant characteristics (age, gender, indication for surgery, type of surgery performed, pain scale used, and outcomes reported).

## Risk of bias and certainty of evidence

The Cochrane Risk of Bias (RoB) 2.0 Tool for Randomized Control Trials was used to evaluate the risk of bias of the included studies, assigning scores as low, high, or unclear in each of the following domains randomization, deviation from the intended intervention, missing data, measurement of outcomes, and selection of outcomes [38]. Scoring was performed independently and in duplicate (ZC, LP), with conflicts resolved by a third reviewer (VA).

Each meta-analyzed outcome was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. They were scored as high, moderate, low or very low based on guidance from the GRADE group, using six pre-specified categories (limitations in study design/RoB, inconsistency of results, directness of evidence, imprecision, publication bias, and other) [39]. This was done to characterize the quality of evidence of the research which contributed to this meta-analysis. The results were then collated in a single summary of findings (SoF) table, highlighting the magnitude of effect and overall grading of evidence for each outcome, as recommended by the Cochrane Collaborative [39]. GradePro software was used to create the SoF table [40].

## Statistical analysis

Given the heterogeneous nature of the included studies in measurement and reporting, only a limited number of data could be pooled; data not pooled are reported qualitatively. The results included in the meta-analysis were SMDs in pain scores and cumulative opioid use at 48 h (both for trials comparing IV acetaminophen to opioids) and proportions for minor adverse events. Statistical analysis was done using the Cochrane Review Manager 5.3 with an alpha of $< 0.05$ [41]. A pairwise meta-analysis was performed with a Dersimonian and Laird random-effects model to estimate the effect size for each outcome if more than two studies reported the result. SMDs with 95% confidence intervals were calculated for pain scores to account for the variability in the scales used. To interpret the SMDs, Cohen's *d* was used, where an SMD 0–0.19 is a trivial effect, 0.20–0.49 is a small effect, 0.50–0.79 is a medium effect, and 0.80 is a large effect [42]. To ease the interpretation, SMDs were back-transformed into the numeric rating scale-11 (NRS-11), allowing the result to be displayed on a scale of 0 to 10. This was done using the standard deviation from Ceelie et al.'s trial, which was considered the most representative [43]. Using standard conversions, cumulative opioid doses were converted into

morphine equivalent doses (MED). In studies where the median and interquartile range were reported, Wan et al.'s standard deviation estimation method was used [44]. For dichotomous outcomes where one arm had no events, a value of 0.4 was used instead of zero, which allowed for calculating the relative risk (RR). For each pooled outcome, heterogeneity was assessed using Higgin's $I^2$ statistic with the following prespecified classifications (0–40%: might not be important, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, 75–100% considerable heterogeneity) [45]. Subgroup analysis was planned for age and type of surgery but was not feasible due to a lack of data. For trials where full were texts unavailable or with unreported data, the study authors were contacted to obtain this data. If the number of patients analyzed was not specifically displayed for each outcome, it was assumed to be the number of patients in each group at baseline.

## Results

### Search results

The search identified 896 citations. After removing duplicates, 805 studies were screened by title and abstract. Title and abstract screening removed 779 irrelevant studies. There was moderate agreement between the reviewers during this phase (95.6% agreement, $\kappa = 0.49$). Twenty-five articles underwent full-text screening. Studies were excluded during full-text screening due to an incorrect study design (5), full text not being available (3), incorrect population (1), duplicate (1), and incorrect intervention (10). Five studies were included in the final analysis. Study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is illustrated in Fig. 1.

### Excluded studies

Several studies initially appeared to meet the inclusion criteria but were excluded. The first was a study by Arora et al., which was an abstract only with no available author contact

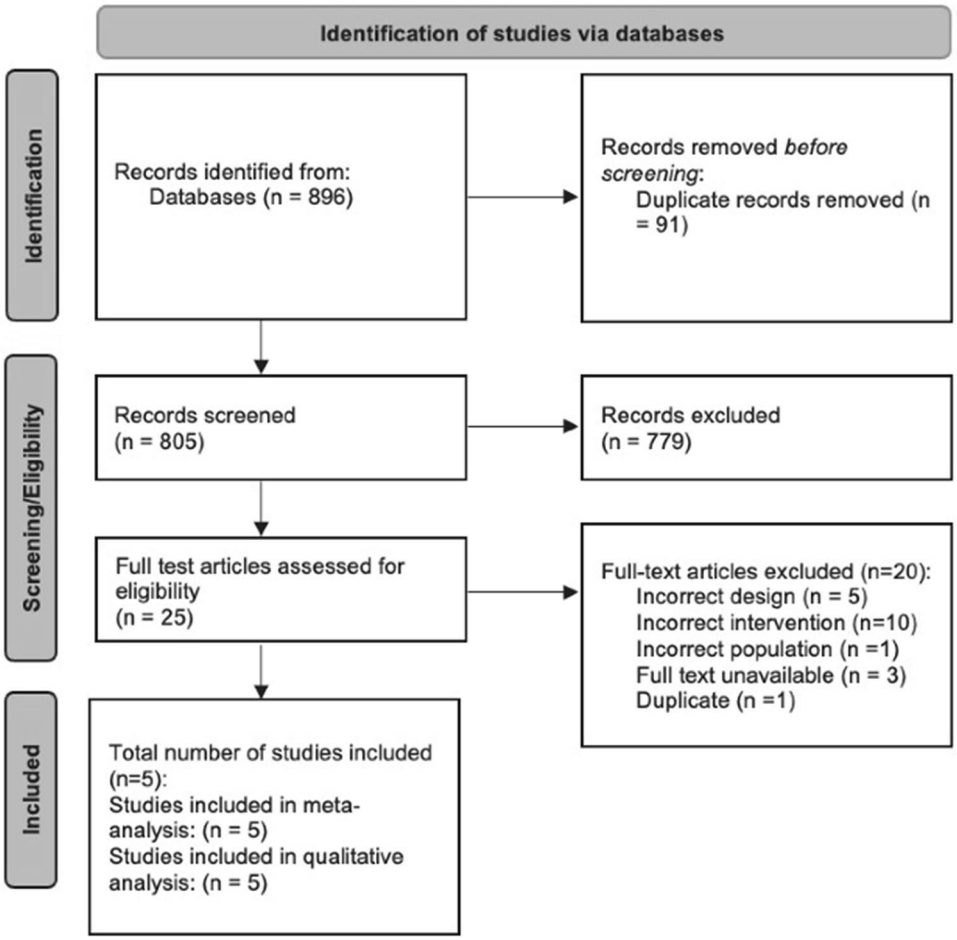


**Fig. 1** Study selection according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines

information [46]. The second was a trial by Majeed et al. where they performed appendectomies; it was not clear from the paper if this was an open or laparoscopic procedure. The study author was contacted with no response [47]. Given the year of publication (2020), the study team felt there was a high chance that these procedures were performed laparoscopically, therefore the study was excluded. The third was a trial by Rugyte et al. in which they reported data from orthopedic and abdominal surgeries [48]. The authors were contacted to provide data only for abdominal surgery, but no response was received; therefore, it was excluded.

## Characteristics of included studies

Five RCTs enrolling a total of 443 patients were included. The pooled mean age of participants was 2.12 years (±2.81). The median number of patients enrolled per study was 66 (range 60–183). The median follow-up time was 48 h (range 6–72). Three studies compared IV acetaminophen to opioids [43, 49, 50]. One of these studies (Ceelie et al.) compared acetaminophen as a primary agent to morphine as a primary agent; however, 66.77% of patients received morphine in the acetaminophen group [43]. As most patients received a combination of opioids and acetaminophen in this trial, it was included with the other two trials comparing IV acetaminophen and opioids to opioids alone. For trials not comparing to opioids, one compared acetaminophen to its prodrug form (propacetamol), and one compared it to a bupivacaine-based epidural [51, 52]. Two studies evaluated only open abdominal surgery [51, 53]. The others evaluated open abdominal and non-cardiac thoracic surgery. Two studies used the visual analogue scale (VAS); otherwise, no common pain scale was used [50, 51]. Overall, there was heterogeneity with comparator pain modalities, outcome measurements, pain scales, and data reporting. A summary of included studies can be found in Table 1.

## Risk of bias

The results of the RoB assessment for each meta-analyzed outcome are displayed in Table 2. There was at least some concern for RoB for each outcome due to inconsistent reporting of randomization and allocation concealment techniques and measurement of outcomes. Our comprehensive search identified only one unpublished manuscript; therefore, the risk of publication bias was not suspected. Funnel plots could not be constructed to further evaluate publication bias as fewer than ten studies were included [45].

## Primary outcome: postoperative pain scores

Given the inconsistent comparisons, it was only possible to pool studies comparing IV acetaminophen to opioids. When pooled, a SMD of -0.20 was found, representing a small decrease in postoperative pain (−0.20, 95% CI −0.76 to 0.35, $p$ 0.47). The 95% CI encompasses both a decrease and increase in pain scores. Back translating this to the NRS-11 scale translates to a decrease of 0.23 points (95% CI −0.88 to 0.40) on a scale of 0 to 10 (with 0 being no pain and 10 being the worst pain). The certainty of the evidence is downgraded due to heterogeneity ($I^2$, 74%), RoB, imprecision, and inconsistency. Therefore, the addition of IV acetaminophen to opioid-based pain regimes may result in little to no difference in postoperative pain scores, but the evidence is very uncertain. The forest plot of this data can be seen in Fig. 2.

Due to a lack of data and variation in recording times, pain scores for time periods before and after 48 h could not be meta-analyzed. Both Dehghan and Hong recorded pain scores up to 48 h; Ceelie et al. only reported pain scores at 48 h [43, 50, 53]. Hong and Dehghan did not identify a statistically significant difference in pain scores at up to 48 h [50, 53]. After 48 h, only Hong et al. recorded pain scores (60 and 72 h) which were non-significantly different [53].

## Primary outcome: postoperative pain scores (IV acetaminophen compared to non-opioids)

Using the Face, Legs, Activity, Cry, Consolability Scale (FLACC, range 0–10), Solanki et al. found that when comparing IV acetaminophen to bupivacaine epidurals, pain scores were statistically significantly lower in the bupivacaine group at multiple time points. When comparing IV paracetamol to propacetamol, Murat et al. used a 10-point VAS scale to assess pain difference and pain relief and found no difference in pain scores in their six hour follow-up.

## Secondary outcome: opioid consumption

Ceelie, Dehghan and Hong et al. recorded cumulative opioid use [43, 50, 53]. When pooled, a mean difference of -1.95 oral MED/kg/48 h (−3.95 to 0.05, $p$ 0.06) was found. Using conservative dosing guidelines for infants less than six months (which represents most patients in these three studies) of 0.08 MED/kg/dose every four hours or the more liberal 0.1 MED/kg/dose every three hours results in a clinical decrease between 1.62 and 2.03 doses of oral morphine equivalents per day. Based on a target minimally clinically important difference of 30% decrease (as used in the sample size calculations by Ceelie and Hong et al.), this is a clinically significant difference. However, the certainty of the evidence is downgraded due to inconsistency ($I^2$, 99%) and imprecision (due to the small sample size). Ultimately, low-quality evidence suggests that IV acetaminophen in conjunction with opioids may reduce opioid use. The forest plot demonstrating this data is available in Fig. 3.

**Table 1** Characteristics of included studies

| | Ceelie | Dehghan | Hong | Murat | Solanki |
|---|---|---|---|---|---|
| Year | 2013 | 2019 | 2010 | 2005 | 2017 |
| Sample Size | 71 | 66 | 63 | 183 | 60 |
| Age | | | | | |
| Control | 20 days (IQR 1.8–87.5) | 16.79 days (SD 15.57) | 17.8 months (SD 10.4) | 4.3 years (SD 2.6) | 40.12 days (SD 45.4) |
| Acetaminophen | 5 days (IQR 1.5–64.5) | 16.67 days (SD 15.77) | 16.9 (SD 8.3) | 4.8 years (SD 2.5) | 42.96 days (SD 68.49) |
| % Male | | | | | |
| Control | 68.4% | NR | NR | 76.1% | 56.6% |
| Acetaminophen | 54.5% | NR | NR | 73.7% | 66.67% |
| Type of surgery | Non-cardiac thoracic (22.5%) and abdominal (77.46%) | Abdominal and thoracic surgery (esophageal atresia, CDH, gastroschisis, duodenal atresia, omphalocele and intestinal obstruction) | Open ureteroneocystostomy | Open inguinal hernia repair | Major thoracic or abdominal (TEF, Thoracotomy, Colostomy, Laparotomy, CDH, EHBA) |
| Follow up (hours) | 48 | 48 | 72 | 6 | 48 |
| Comparison | IV Morphine | IV Fentanyl | IV Fentanyl PCA | Propacetamol | Bupivacaine epidural |
| Pain scale | NRS 11 and COMFORT-B | NIPS | CHEOPS | VAS (OPS if child unable to do VAS) | FLACC |
| Opioid use recorded | Yes | Yes | Yes | No | No |
| Secondary outcomes | Urinary retention, bradycardia, apnea, reintubation, time on ventilator other medications required | Duration of intubation | Nausea and vomiting, pruritus, poor oral feeding, sedation, desaturations | Nausea, vomiting, injection site pain, hypotonia, abdominal pain/reaction, fever, other medications required | Sedation, bradycardia, vomiting, delayed recover, cardiac arrest |

*IQR* interquartile range, *SD* standard deviation, *NR* not reported, *NIPS* neonatal infant pain scale, CHEOPS: children's hospital of eastern ontario pain scale, *VAS* visual analogue scale, *OPS* objective pain scale, *FLACC* face, legs, activity, cry, consolability Scale, *TEF* tracheoesophageal fistula, *CDH* congenital diaphragmatic hernia, *EHBA* extrahepatic biliary atresia

**Table 2** Cochrane risk of bias assessment 2.0 for meta-analyzed outcomes

| | Randomization | Deviation from intended intervention | Missing outcome data | Measurement of outcomes | Selection of reported results | Overall risk of bias |
|---|---|---|---|---|---|---|
| Postoperative pain scores | | | | | | |
| Ceelie 2013 | Low | Low | Low | Low | Low | Low |
| Dehghan 2019 | Some concern | Low | Low | High | Low | High |
| Hong 2010 | Low | Low | Low | Low | Low | Low |
| Opioid consumption at 48 h | | | | | | |
| Ceelie 2013 | Low | Low | Low | Low | Low | Low |
| Dehghan 2019 | Some concern | Low | Low | Low | Low | Some concern |
| Hong 2010 | Low | Low | Low | Low | Low | Low |
| Minor adverse events | | | | | | |
| Ceelie 2013 | Low | Low | Low | Some concern | Low | Some concern |
| Dehghan 2019 | Some concern | Low | Low | High | Some concern | High |
| Hong 2010 | Low | Low | Low | Low | Low | Low |

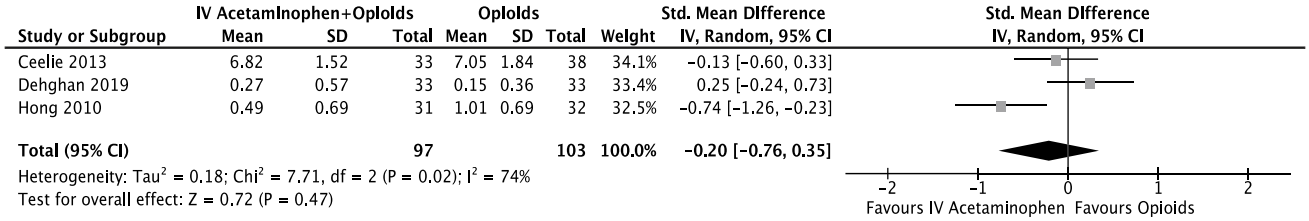


**Fig. 2** Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone presented as standard mean differences in postoperative pain scores

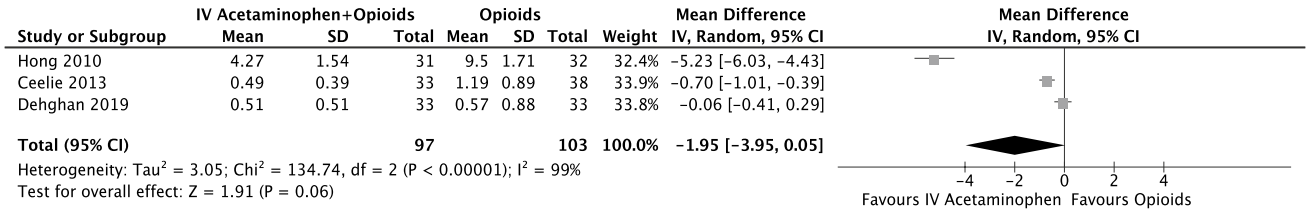


**Fig. 3** Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone for opioid consumption presented in morphine equivalent doses/kg/48 h

Only Hong et al. examined cumulative opioid use beyond 48 h [53]. They found that from 48 to 72 h, there was a difference in 6.1 mcg/kg/24 h of fentanyl use, but this difference was not significant (*p* 0.357).

## Secondary outcome: minor adverse events (IV acetaminophen compared to opioids)

Due to the heterogeneity in the comparators of the included trials, it was not methodologically feasible to pool the data from all studies. Therefore, minor adverse events from the studies comparing IVA to opioids were aggregated. Minor adverse events included nausea, vomiting, apnea (with and without naloxone administration) and urinary retention. Pooling demonstrated a reduction in minor adverse events (RR 0.39, 95% CI 0.11 to 1.43, – 0.15), with an absolute reduction of 207 fewer per 1000 (95% CI from 302 fewer to 146 more). The $I^2$ of 0% indicates low levels of heterogeneity. The quality of evidence was downgraded due to RoB, inconsistency, and imprecision and is upgraded due to the large effect size. Therefore, there is low-quality evidence suggesting

that the addition of IV acetaminophen may reduce minor adverse events. The results of this analysis, represented as a forest plot, can be seen in Fig. 4.

### Secondary outcome: other adverse events (IV acetaminophen compared to non-opioids)

When Solanki et al. compared IV acetaminophen to a bupivacaine epidural, there were significantly higher sedation scores at multiple time points in the IV acetaminophen group compared to the epidural group [52]. Solanki et al. also found more bradycardia in the epidural group (5/30 vs. 0/30, $p < 0.05$). However, they did report that all bradycardia was asymptomatic and successfully managed with anticholinergics [52]. Murat et al. found IV paracetamol to have less injection site pain (14/95 vs. 29/88, $p$ 0.005) than propacetamol but otherwise did not find a difference with any other adverse events [54].

### Secondary outcome: other adverse events (IVA compared to opioids)

Ceelie et al. found no difference in adverse events (9/33 vs. 11/38, $p$ 0.875). Specifically, they did not find a difference in reintubation rates (1/33 vs. 2/38, $p$ 0.444) or bradycardia (6/33 vs 7/38, $p$ 0.979) [43]. Dehghan et al. found no difference in the duration of intubation between the acetaminophen and fentanyl groups ($6.76 \pm 10.34$ vs $7.82 \pm 14.48$ h, $p$ 0.733) [50]. Hong et al. found significantly less sedation in the IV acetaminophen arm compared to the fentanyl arm (3/31 vs. 15/32, $p$ 0.019). They found no difference in pruritus (2/31 vs. 3/32, $p$ 0.515) or poor oral feeding (0/31 vs. 4/32, $p$ 0.060) [53].

### Unreported outcomes

Additional outcomes selected a priori for analysis, including LoS, ileus, and time to enteral feeds, were not reported by any author.

### Summary of findings

The GRADE SoF table summarizing the results of the meta-analysis can be found in Table 3. Footnotes are included to indicate the rationale for down or upgrading the certainty of evidence.

## Discussion

Due to the limited number of studies and significant heterogeneity in outcomes, it is impossible to draw firm conclusions about IV acetaminophen's role in postoperative pain control in pediatric patients. When studies compared IV acetaminophen to opioids, the analyses suggested there may be little to no difference in pain scores and a decrease in opioid consumption and minor adverse events. In isolation, the lack of change in postoperative pain scores with the addition of IV acetaminophen may appear to provide evidence against its use. However, when viewed in concert with its ability to reduce opioid use and adverse events without sacrificing pain management, it can be viewed as an important adjunct to postoperative pain management. When IV paracetamol was compared to propacetamol, it demonstrated no difference in pain scores, but paracetamol was associated with less injection site pain. When IV acetaminophen was compared to bupivacaine epidurals, the data demonstrated decreased pain scores with epidural use, with no change in adverse events aside from bradycardia.

Each trial included or allowed additional rescue medication for pain, making it difficult to assess if IV acetaminophen is suitable as a single agent. Notably, Ceelie et al. reported that 66.77% of patients assigned IV acetaminophen alone required rescue opioids, indicating it is inadequate as a single agent for major surgery [43]. However, the rates of rescue morphine for the morphine group were not significantly different at 60.5% ($p$ 0.59), which provides a more nuanced analysis that no single agent is suitable for postoperative pain control after major surgery in infants, which helps to support the implementation of multi-modal pain control regimes in these populations.

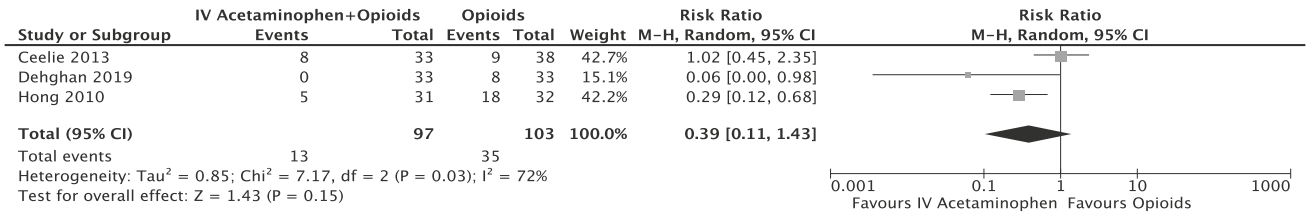


**Fig. 4** Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone for minor adverse events (nausea, vomiting, urinary retention, apnea)

**Table 3** Summary of findings for IV acetaminophen and opioids compared to opioids alone for postoperative pain management

| Outcomes | No of participants (studies) follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with opioids alone | Risk difference with IV acetaminophen and opioids |
| Standard mean difference in postoperative pain score at 48 hours presented on NRS-11 scale of 0–10 (0 being no pain, 10 being worst pain) | 200 (3 RCTs) | ⨁◯◯◯ Very low[a,b,c] | – | | MD 0.23 lower (0.88 lower to 0.40 higher) |
| Opioid consumption (MED/kg/48 h) | 200 (3 RCTs) | ⨁⨁◯◯ Low[d,e] | – | The mean opioid was 3.75 MED/kg/48 h | MD 1.95 MED/kg lower (3.95 lower to 0.05 higher) |
| Minor adverse events follow-up: range 48 to 72 h | 200 (3 RCTs) | ⨁⨁◯◯ Low[f,g,h] | RR 0.39 (0.11 to 1.43) | 340 per 1,000 | 207 fewer per 1,000 (302 fewer to 146 more) |

Patient or population: pediatric patients after open abdominal or thoracic surgery, Setting: inpatients, Intervention: IV acetaminophen and opioids, Comparison: opioids alone

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

*NRS-11* numeric rating scale 11, *MED* morphine equivalent doses, *CI* confidence interval, *MD* mean difference, *RR* risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Concerns with allocation concealment and appropriateness of the scale used to measure pain (NIPS) lead to an overall high risk of bias for Dehghan et al.

[b]Variability in point estimates, with minimal overlap of confidence intervals. $I^2$ statistic of 74%, with $p$-value of 0.02. Heterogeneity in populations (ages and procedures) and co-interventions may account for some of this heterogeneity

[c]SMD of 0.2 was selected for the minimal clinically important difference (MCID) based on Cohen's delta. Using this MCID, optimal information size criteria is not met, and effect estimate with confidence interval demonstrates appreciable benefit or harm

[d]Wide variance between point estimates, with minimal overlap of confidence intervals. $I^2$ statistic of 99%, with a $p$-value of $<0.001$. Heterogeneity in populations (ages, procedures) and based on local prescribing practices may account for this heterogeneity

[e]Using the threshold of a 30% reduction in MED/kg/48 h used by Ceelie et al. and Hong et al. in their sample size calculation, the difference identified in this meta-analysis is a clinically significant reduction, however; the optimal information size criterion is not met

[f]Concerns for bias in lack of consistent definition of outcome measures and reporting and lack of clear allocation concealment in Dehghan et al.

[g]There is some variation in point estimates (notably Dehghan et al.), however confidence intervals overlap. $I^2$ of 72% ($p$ 0.03) indicates substantial heterogeneity

[h]Optimal information size criteria is not met. Using a threshold of a 13% reduction (based on other trials adverse events), the difference identified is clinically significant, with the confidence intervals encompassing potential benefit and no difference and excluding potential harm

Adverse events, including urinary retention, duration of intubation, reintubation, apnea, and bradycardia, were reported infrequently and could not be individually pooled. In addition, other relevant outcomes such as LoS, time to first enteral feed, and time to first bowel movement were not reported.

An unanticipated finding was that only one eligible trial assessed children over 24 months. The reason for this limited age range is not entirely clear; however, it may be that IVA remains unapproved for use in patients under 24 months and that clinicians are eager to understand if there may be enough benefit to warrant its approval in this demographic. This does limit our findings to being applicable to only patients less than 24 months in age.

## Limitations of the evidence and of the review

There are multiple limitations associated with this meta-analysis that must be considered. The methodologic decision to include only RCTs resulted in a smaller sample size. It is unclear how this may have affected the results; however, the risk of bias associated with including low-level evidence was felt to be significant enough to warrant excluding them so as not to bias results. Similarly, a decision was made to focus this review on open non-cardiac-thoracic and abdominal procedures due to the different physiology and management compared to other types of pain and surgery. This revealed that most literature on IV acetaminophen was done in non-surgical settings or during minor procedures, demonstrating a need for further research. Another methodologic limitation was the choice to include multiple pain control comparators (opioids, pro-drugs, epidurals), which made pooling difficult due to inconsistency.

Not only were there a limited number of trials included, but each trial included a limited number of participants, with the largest being 180 [51]. Small sample sizes lead to more significant uncertainty surrounding point estimates and greater uncertainty in the results of this meta-analysis [55]. The $I^2$ statistics for the meta-analysis of pain and opioid use were relatively high, particularly for opioid use (99%); these results must be interpreted cautiously. Large, adequately powered studies are required. There was significant heterogeneity in pain scales, pain modalities assessed, and secondary outcomes. This heterogeneity limited conducting meta-analyses that included all trials or other important secondary outcomes. There were also concerns about the high RoB of the included studies, limiting the analysis due to bias. Due to the limited sample size and variability in the available data, it was impossible to perform the pre-planned subgroup analyses to evaluate the unique impact IV acetaminophen might have based on age and type of surgery and over time.

Pain reporting is subjective by nature, which represents another limitation. This subjectivity is compounded in pediatrics, where many patients are not developmentally capable of reporting their pain, and a guardian or clinician reports their experience of pain. The bias associated with pain scores in pediatrics cannot be wholly avoided. However, it can be mitigated by using validated scales appropriate for the age and scenario, including objective components (such as vital signs), blinded outcome assessors, and multiple scales and assessors to ensure inter-test reliability and inter-rater reliability [56–58].

## Future directions

This field requires more large-scale RCTs to increase the sample size and, thus, precision. A uniform lack of patient-centric designs limits the existing data. Many patient-important outcomes related to abdominal and non-cardiac-thoracic surgery and opioids (i.e., LoS, gastrointestinal function, urinary retention, and oxygen/ventilatory support requirements) were sparsely reported. These variables are important contributors to the LoS, are patient-important, and require further attention. Furthermore, the longest follow-up period was 72 h; however, after major surgery, pain persists beyond 48–72 h and does not capture the entire recovery period. Including longer follow-up would help clarify when IV acetaminophen could be most effectively used during the recovery period. This topic requires specific analysis in pediatric patients of various ages to understand best how it may uniquely benefit different age groups. More work is required comparing IV acetaminophen to non-opioid medications.

## Conclusions

Mounting evidence details the short- and long-term consequences of opioid exposure in pediatrics. Therefore, research evaluating how to reduce this exposure is paramount [7, 8]. The available evidence suggests that in children less than 24 months when IV acetaminophen is added to opioid-based postoperative pain regimes, there may be no difference in postoperative pain scores and a decrease in opioid consumption and minor adverse events. However, the evidence is very low to low quality. There is insufficient evidence to conclude how IV acetaminophen compares to other modalities or its effects in children older than 24 months. More high-quality, patient-centric research is required to confirm these results.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00383-022-05282-0.

**Author contributions** All authors contributed to the study conception and design. V.A. completed the literature search. V.A., Z.C., and L.P performed data collection and analysis. Conceptualization, methodology, and supervision were performed by J.M.W. and D.B. The original draft of the manuscript was written by V.A. All authors participated in review and editing.

**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Competing interests** The authors declare no competing interests.

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