South African National Department of Health
Review Report
Component: Treatment of Peri-operative Pain in Children

TITLE: Intravenous Paracetamol for the treatment of peri-operative pain in children where oral route cannot be used
DATE: June 2022

Key findings

- Oral paracetamol is currently indicated for peri-operative pain in children and rectal paracetamol is the listed alternative if the child is unable to take oral medication. Intravenous (IV) paracetamol is a potential alternative for this patient group.
- We conducted a review of systematic reviews, meta-analyses and clinical trials reporting on the efficacy and safety of IV paracetamol for peri-operative pain in children.
- In February 2022, a literature search was conducted using PubMed, Cochrane Database and Epistemonikos.
- After applying pre-specified inclusion and exclusion criteria, we identified 3 randomized clinical trials for review, which enrolled a total of 262 children aged between 6 months and 10 years.
- Most studies included had small samples sizes. Overall, we are uncertain if intravenous (IV) or rectal paracetamol are superior in terms of efficacy:
  - Pain intensity after surgery in children; one RCT found no difference at all times assessed after extubation between groups. Another RCT also found no difference except for at 4 and 6 hours post extubation, where a mean difference in favour of rectal paracetamol was observed (2 RCTs, n=126, very low quality).
  - Time to first analgesia required in children after surgery; two RCTs reported longer mean times to requiring first analgesia in rectal paracetamol groups however not all statistics/values were provided in the studies and samples sizes were small (n=166, very low quality).
  - Need for analgesia post-surgery after the recovery room in children; both RCTs reported a difference in favour of rectal. However, one RCT did not provide a p value, and another RCT provided a p value but not the point estimates which made it hard to assess with the results with certainty (2 RCTS, n=142, very low quality).
- No significant adverse events were reported in any study for rectal or IV paracetamol in children. However, the pharmacokinetics of paracetamol following rectal administration are highly variable.
- IV paracetamol is less costly than rectal paracetamol.

Summary of findings: IV paracetamol compared to Rectal paracetamol for perioperative paediatric patients in need of analgesia

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Pain intensity at recovery assessed with: standard paediatric pain scores (CHIPPS 4-point scale or FLACC 10-point scale)	Total number 152 (78 in each group) Haddadi et al: n=96, mean difference 0.43 on CHIPPS scale (in favour of rectal) 95% CI [-0.46 - 1.32], P=0.333 Khalili et al: n=120, mean difference 0.5 on FLACC scale (in favour of IV) reported as not significant but P value not reported)	156 (2 RCTs)	⊕◯◯◯ Very low[a,b,c]
Pain intensity 6 hours after extubation assessed with: standard paediatric pain scores (CHIPPS 4-point scale or FLACC 10-point scale)	Total number 152 (78 in each group) Haddadi et al: n=96, mean difference 0.63 on CHIPPS scale (in favour of rectal), 95% CI [0.12 - 1.14], P= 0.019 Khalili et al: n=120, mean difference 0.2 on FLACC scale (in favour of IV), CI [- 0.303 -(-)0,10] P=reported as not significant but P value not reported)	156 (2 RCTs)	⊕◯◯◯ Very low[a,b,c]
Pain intensity 12 hours after extubation assessed with: standard paediatric pain scores (CHIPPS 4-point scale or FLACC 10-point scale)	Total number 152 (76 in each group) Haddadi et al: n=96, mean difference 0.23 on CHIPPS scale (in favour of rectal), 95% CI [-0.07 - 0.53], P= 0.408 Khalili et al: n=120, mean difference 0.2 on FLACC scale (in favour of IV), CI [-0.28 - 0.12], reported as not significant but P value not reported)	156 (2 RCTs)	⊕◯◯◯ Very low[a,b,c]
Time to first required analgesia postoperatively	Total number 142 (71 in each group) Capici et al: n=46, median difference of 3 hours (in favour of rectal), P=0.0.1 Haddadi et al: n=96, mean difference of 1.15 hours (in favour of rectal), P value not reported	142 (2 RCTs)	⊕◯◯◯ Very low[a,c]
Number of children requiring analgesia after the recovery room	Total 142 (71 in each group). Capici et al - in favour of rectal, P value not reported, RR 1,02 95% [CI 0.68 - 1.55]. Khalili et al - significant difference reported in favour of rectal but P value or absolute numbers not provided	(2 RCTs)	⊕◯◯◯ Very low[a,c,d]

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.

Explanations
a. Downgraded by one level for risk of bias: Unclear risk for reporting and selection bias for both studies
b. Downgraded by one level for unexplained inconsistent results. Each trial favors a different route of administration, but there are also different age children undergoing different procedures - it is not clear which of these factors may impact the results.
c. Downgraded by two levels for imprecision: very small sample size
d. Unable to assess - unable to calculate CIs, both show effect in same direction

1. Executive Summary: Paracetamol, IV – Peri-operative pain

Date: June 2022
Medicine (INN): Paracetamol, IV
Medicine (ATC): N02BE01
Indication (ICD10 code): G89.18 – Acute peri-operative pain
Patient population: Peri-operative paediatric patients in need of analgesia where oral route not available
Prevalence of condition: n/a
Level of Care: Hospital level
Prescriber Level: Anaesthesiologist, anaesthetist, surgeon, medical officer
Current standard of Care: Rectal paracetamol
Efficacy estimates: (preferably NNT): The certainty of evidence is very low and is limited to small studies: See Summary of Findings Table.
Motivator/reviewer name(s): Kim MacQuilkan, Anisa Bhettay, A Hohlfeld, Jane Riddin, Milli Reddy
Acknowledgement: Tamara Kredo

2. Name of Reviewers

Ms Kim MacQuilkan, Dr Anisa Bhettay, Mr A Hohlfeld, Dr Jane Riddin and Dr Milli Reddy

3. Author Affiliation and Conflict of Interest Details

- Ms K MacQuilkan (Better Health Programme South Africa) has no interests to declare.
- Dr A Bhettay: Department of Anaesthesia and Perioperative Medicine, Division of Paediatric Anaesthesia, Red Cross War Memorial Children's Hospital – Drafting of external guidelines for procedural sedation, bronchospasm, pain, malignant hyperthermia, local anaesthetic toxicity, regional anaesthesia – no financial benefit.
- Mr A Hohlfeld (Cochrane South Africa, South African Medical Research Council) has no interests to declare.
- Dr J Riddin (Affordable Medicines Directorate, National Department of Health) has no interests to declare
- Dr M Reddy (Better Health Programme South Africa) has no interests to declare.
- Dr T Kredo (Cochrane South Africa, South African Medical Research Council (SAMRC) and Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network) has no interests to declare.

4. Introduction/Background

The peri-operative period is a significant period for the management of pain in paediatric patients. Optimal peri-operative pain management is important to reduce post-operative complications, enhance recovery after surgery, and shorten the length of hospital stay(1). Management of peri-operative pain, in children, has largely relied on the use of opioid analgesics and non-steroidal anti-inflammatory drugs(2–5). However, opioids are being used less often because of significant adverse effects, such as respiratory depression, nausea, vomiting, slowed gastrointestinal function, and sedation(6,7). Adequate pain control and risk of adverse events remain challenging within the paediatric population due to limited evidence for the use of analgesics in this vulnerable population. Paracetamol has been established as a safe analgesic and the Paediatric Hospital Level Standard Treatment Guidelines (STGs) currently recommend oral paracetamol for peri-operative pain, with oral ibuprofen as an alternative or optional addition. Non-steroidal anti-inflammatory drugs (NSAIDs) are not indicated for use in children under 3 months and are contraindicated in a variety of clinical scenarios where paracetamol can be safely utilised.

Currently the STGs recommend rectal paracetamol if the oral route is unavailable in the peri-operative period, however paracetamol suppositories are not currently on tender and pharmacokinetic studies indicate that the pharmacokinetics of paracetamol following rectal administration are highly variable and unpredictable (varying 25-100%) (20–22). Furthermore, rectal paracetamol cannot be administered to children under 3 months. Intravenous (IV) paracetamol is effective and safe for peri-operative analgesia in children of all ages including newborns[1] and is indicated for the management of peri-operative pain across various surgical procedures such as tonsillectomy, strabismus surgery and dental restoration (2,3,6,8–11). The National Essential Medicine List (NEMLC) Paediatric Expert

[1] Accord Package Leaflet for Paracetamol 10mg/ml Solution for Infusion

Review Committee (PERC) has therefore conducted a review of IV paracetamol for the treatment of peri-operative pain in children when the oral route is not possible. The objective of this review is to assess the evidence for efficacy and safety of IV paracetamol in the management of peri-operative pain in children for this clinical situation.

5. Purpose/Objective

Research Question

How effective and safe is intravenous paracetamol as an analgesic for peri-operative pain where the oral route is not available, compared to rectal paracetamol, in paediatric patients who are undergoing surgery? Table 1 outlines the scope of this medicine review.

Table 1. Scope of the technical review

Population	Perioperative paediatric patients in need of analgesia who are unable to use the oral route
Intervention/s and comparisons	Intervention: intravenous paracetamol Comparator: rectal paracetamol
Outcomes	**Outcomes:** - Pain intensity - Pain relief - Time to achieve pain relief - Need for rescue medication (number of participants requiring rescue medication and time to using rescue medication) - Use of opioids - Adverse effects/ adverse events - Serious adverse events
Study designs	Systematic reviews or meta-analyses or randomised controlled trials (RCTs) or case-control studies or cohort studies Clinical practice guidelines

6. Methods

A search was conducted using the PubMed, Cochrane and Epistemonikos databases on 1 February 2022. Appendix 1 outlines the search strategy. The search was open to systematic reviews, meta-analyses and RCTS. Only studies matching the PICO questions outlined above were included. The search and inclusion/exclusion of articles were completed in duplicate by two reviewers (KM and JN). Differences in opinion were resolved through discussion. We included studies of IV paracetamol compared to rectal paracetamol (the listed alternative). Studies comparing IV to oral paracetamol or placebo were excluded. Data from included studies was extracted and included in narrative and summary format. One reviewer summarised the included articles and a second reviewer checked the results. Risk of bias for each included RCT was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Version 1[2]). GRADEing of evidence for each outcome of interest was conducted in collaboration (KM, AH and TK[3]). In addition, a search for relevant clinical practice guidelines was completed using the following databases: World Health Organization (WHO), Guidelines International Network (GIN), National Institute for Health Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN). One reviewer used simple, broad search terms, including 'paracetamol', 'post-operative', 'pain', 'children' in the electronic searches for clinical guidelines. Included guidelines were appraised utilising the AGREE II checklist by two reviewers (KM and JN).

[2] Higgins J P T, Altman D G, GÃ¸tzsche P C, JÃ¼ni P, Moher D, Oxman A D et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011; 343 :d5928 doi:10.1136/bmj.d5928

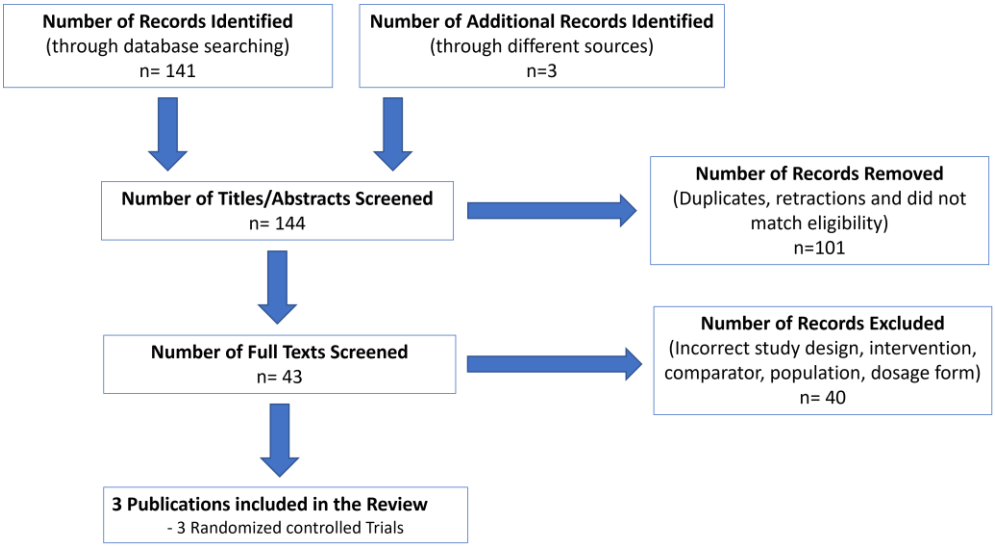
[3] Cochrane GRADEing Group. Cochrane Methods GRADEing. Available: https://methods.cochrane.org/gradeing/

7. Results

Research studies

One hundred and forty-one articles were identified (138 PubMed, 1 Cochrane, 2 Epistemonikos). A further three articles were identified through checking reference lists of eligible reviews. Titles were screened for duplicates and three articles were removed. Two articles had been retracted. Exclusion principles from PICO were applied to titles and abstracts and a further 96 articles excluded. Forty-three full text publications were reviewed. Forty studies were excluded and three studies (all randomized controlled trials) were included in the final review. No meta-analyses or systematic review satisfied the inclusion criteria and matched the PICO. Articles within identified systematic reviews and meta-analyses that did fit the PICO were included. Table 2 summarises the characteristics of the included studies. See Appendix 2 for details on the excluded studies.

Figure 1: Prisma Diagram of Selection of Studies



The findings of the included publications are outlined below in a narrative and summarized in Table 2.

Description of included studies

Three studies were included in the review

- A double-blind randomised controlled trial by Capici *et al*. (2008) conducted in 46 children aged 2-5 years old, undergoing adenoidectomy or adenotonsillectomy. The RCT compared pre-operative (after induction) intravenous paracetamol to rectal paracetamol, with the primary outcome of time to first analgesia post-operatively(15).
- A double-blind randomised controlled trial by Hadaddi *et al*. (2014) conducted in 96 children aged 4-10 years old, undergoing adenotonsillectomy surgery. The RCT compared preoperative (after induction) intravenous paracetamol to rectal paracetamol on outcomes of time to first analgesia and post-operative pain(16).
- A double-blind randomised controlled trial by Khalili et al. (2016) on 120 children aged 6 months to 6 years old, undergoing inguinal herniorrhaphy surgery. The RCT compared pre-operative (after induction) intravenous paracetamol to rectal paracetamol and placebo, with the primary outcome of post-operative pain(1).

Effectiveness and safety of the intervention

COMPARISON 1: Intravenous paracetamol 10mg/kg (16) **OR 15 mg/kg** (1,15) **vs rectal paracetamol 15mg/kg** (16) **OR 40 mg/kg** (1,15) **[1 trial, n=46 children, IV 15mg/kg vs rectal 40mg/kg**(15)**, 1 trial, n = 96 children, IV 10mg/kg vs rectal 15mg/kg** (16)**, 1 trial, n=120, IV 15mg/kg vs rectal 40mg/kg** (1)**]**

Pain intensity [1 trial, n=96(16), 1 trial, n=120(1)]

- The evidence regarding the difference in postoperative pain intensity between IV and rectal paracetamol is very uncertain (very low quality for all outcomes under pain intensity):
  - **Pain assessment by standard paediatric scales at recovery** – There may be little to no difference between IV and rectal paracetamol in pain intensity at recovery measured with paediatric pain scales. One RCT reported a lower mean on CHIPPS scale for rectal paracetamol compared to IV (MD 0.43 points lower, 95% CI [-0.46 - 1.32], P=0.333), n=96 (16). Another RCT reported a lower mean on FLACC scale in the IV paracetamol group compared to rectal paracetamol (MD 0.5 points lower, reported as not significant but P value not reported), n=120(1).
  - **Pain assessment by standard paediatric scales at 2 hours after extubation** – There may be little to no difference between IV and rectal paracetamol in pain intensity at 2 hours after extubation measured with paediatric pain scales. One RCT reported a smaller mean on CHIPPS scale for rectal paracetamol compared to IV (MD: 0.39 points lower 95% CI [-0.04 - 0.82], P=0.071), n=96 (16). Another RCT reported a lower mean on FLACC scale in the IV paracetamol group compared to the rectal (MD 0.3 points lower, reported as significant but P value not reported), n=120(1).
  - **Pain assessment by standard paediatric scales at 4 hours after extubation** – There may be little to no difference between IV and rectal paracetamol in pain intensity at 4 hours after extubation measured with paediatric pain scales. One RCT reported a lower mean on CHIPPS scale for rectal paracetamol (MD 0.71 95% CI [0.26 – 1.16], P=0.003), n=96 (16). Another RCT reported a lower mean on FLACC scale in favour of IV paracetamol (MD 0.2, reported as not significant but P value not reported)(1), n=120.
  - **Pain assessment by standard paediatric scales at 6 hours after extubation** – There may be little to no difference between IV and rectal paracetamol in pain intensity at 6 hours after extubation measured with paediatric pain scales. One RCT reported a lower mean on CHIPPS in favour of rectal paracetamol (MD 0.63 95% CI [0.12 - 1.14], P=0.019), n=96 (16). Another RCT reported a lower mean on FLACC in favour of IV paracetamol, reported as not significant but P value not reported) n=120 (1) .
  - **Pain assessment by standard paediatric scales at 12 hours after extubation** – There may be little to no difference between IV and rectal paracetamol in pain intensity at 12 hours after extubation measured with paediatric pain scales. One RCT reported a lower mean on CHIPPS in favour of rectal paracetamol (MD 0.23 95% CI [-0.07 - 0.53], P= 0.408), n=96 (16). Another RCT reported a lower mean on FLACC in favour of IV paracetamol (MD 0.2, reported as not significant but P value not reported), n=120(1).

Postoperative analgesic use [1 trial, n-46 (15), 1 trial, n=96(16), 1 trial, n=120(1)]

- The evidence regarding the difference in postoperative analgesic use between IV and rectal paracetamol is very uncertain (very low quality):
  - **Time to first postoperative analgesia** – There may be little to no difference in time to first analgesia. One RCT reported a lower median in hours in the rectal paracetamol group (Median difference 3 hours, IQR not provided, P=0.01), n=46(15). Another RCT reported a lower mean time in hours in favour of rectal paracetamol (MD 1.15 hours, P value not reported), n=96(16).
  - **Number of children requiring rescue analgesia in recovery** – There may be little to no difference in number of children requiring rescue analgesia in recovery. One RCT reported only 1 child requiring rescue analgesia in the IV paracetamol group and no children in the rectal group, P value not reported), n=46 (15).
  - **Number of children requiring rescue analgesia after recovery room** – There may be little to no difference in number of children requiring rescue analgesia after the recovery room. One RCT reported that one less child required analgesia in the rectal paracetamol group (Rectal group – 22, IV group 23, P value not reported), n=46 (15). Another RCT, reported that use of analgesics was higher in the IV group compared to the rectal group (P=0.0001, numbers not reported), n=96 (16).

The tables below summarises the evidence for the three publications included in this review.

Table 2: Characteristics of Included Studies for comparisons of paracetamol dosage forms

Citation	Study design	Population (n)	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
Capici *et al 2008* (15)	A double-blind randomized controlled trial	N=46 children; with ASA physical status I–II, aged 2–5 years, weighing < 30 kg; scheduled for elective adenoidectomy or adenotonsillectomy.	***Intravenous versus rectal paracetamol*** *1) Preoperatively (after induction) - intravenous paracetamol, 15mg.kg-1* *OR* 2) *Preoperatively (after induction) - rectal paracetamol 40mg.kg^{-1}* Rescue analgesia in recovery room bolus of fentanyl 0.5mg.kg^{-1} Rescue analgesia after recovery room paracetamol 20mg.kg^{-1} rectally	**The primary outcome was time to first rescue analgesia** Time to first analgesia and total analgesia use Time to first rescue analgesia was defined as time from tracheal extubation to the first request or indication for supplemental analgesia because of Children and Infants Postoperative Pain Scale (CHIPPS) score > 4. • Time to first analgesic request was longer in children receiving rectal paracetamol (median 10 h, inter-quartile range 9–11 h) compared with those receiving intravenous (7, 6–10 h) (P-value 0.01 by log-rank test for equality in survivor function - **significant**). Very few children needed rescue analgesia in the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h. • No differences reported between number of children requiring rescue analgesic in the recovery room (1 in the IV group versus 0 in the rectal group) and after the recovery room (23 in IV group and 22 in the rectal group) – **P value not reported.** Emergence agitation Four-point agitation scale: (1) calm child, no intervention required; (2) consolable child, requires only physical contact with the parents; (3) agitated child, a screaming and crying child; and (4) aggressive child, must be physically restrained in order to avoid harm. Significant postoperative agitation defined as an agitation scale 3 or 4. • There were no substantial differences in incidence of postoperative agitation; 8 (35%) in the rectal group versus 11 (48%) in the intravenous group defined to have significant agitation – **P value not reported**. Child's comfort at home Scale designed to assess recovery after adenotonsillectomy comprising six separate measures: spontaneous pain and pain at swallowing (verbal scale 0–4 each), occurrence of PONV (0 or 1), disturbed feeding (0 or 1), sleep (0 or 1), and play (0 or 1). A total score of 4 or less points is considered as very satisfactory.	**Limitations include:** • Small sample (46) • Rescue medication same as treatment arm which may have impacted the at home measurement. • All statistics on primary outcome not reported – only graph included. ***Author's Conclusions:*** Rectal acetaminophen 40 mg.kg^{-1} provides longer analgesia for moderately painful procedures when compared with 15 mg.kg^{-1} acetaminophen IV. ***Risk of Bias*** ***Random Sequence Generation (Selection Bias)***: Randomisation but method not described – **Unclear Risk** ***Allocation Concealment (Selection Bias)***: Not described – **Unclear Risk** ***Blinding of Participants and Personnel (Performance Bias)***: medication given after induction - **Low Risk** ***Blinding of Outcome Assessment (Detection Bias)***: "Pain was assessed by a number of different nurses and anaesthetists who were all familiar with the CHIPPS scale and all unaware of treatment allocation" - **Low Risk** ***Incomplete Outcome Data (Attrition Bias)***: 2 subjects in each of the IV and rectal groups (1 double dose of rectal, 3 did not receive fentanyl during induction – **Low risk** (9% of IV group) ***Selection Reporting (Reporting Bias)***: Not all outcome statistics provided - **Unclear Risk**

Citation	Study design	Population (n)	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
				• There was no evidence for any difference between the groups in the score of comfort at home; 14 children (61%) in the IV group and 18 children (78%) in rectal group scored four or less points (p=0.3) – **not significant**.	***Other Bias***: No other detected - **Low Risk**

Citation	Study design	Population (n)	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
Haddadi et al. 2014 (16)	A double-blind randomized controlled trial	N=96 children, aged 4–10 years, scheduled for elective adenotonsillectomy.	***Intravenous versus rectal paracetamol*** 1) *Preoperatively (after induction) - intravenous paracetamol, 10mg/kg* *OR* 2) *Preoperatively (after induction) - rectal paracetamol 15/kg* Rescue analgesia intravenous pethidine 0.5 mg/kg	**Primary outcome of time to first analgesia and post-operative pain** Analgesia use • Use of analgesics was significantly higher in the IV group compared to rectal group (P=0.0001 - **significant)** – **number not reported.** • Time to first additional dose of analgesia was shorter in the rectal group 4.96 versus 3.81 hours – **however significance not reported** Postoperative pain – Pain intensity Assessed based on children and infants postoperative scales (CHIPPS) criteria • Both groups had statistically significant lower mean scores at 2-hour intervals over the study period (IV group P=0.0001 – **significant;** Rectal group P=0.0001 **- significant**). • At recovery, 2 hours, 12 hours, 18 hours and 24 hours post-surgery mean scores were slightly lower in the rectal group compared to the IV group but mean differences between groups were not statistically significant (P=0.333, P=0.071, P=0.408, P=0.276, P=0.562 respectively – **not significant**). • At 4 hours post-surgery, mean scores were significantly lower in the rectal paracetamol group (IV group 2.68; rectal group 1.97; P=0.003 - **significant**). • At 6 hours post-surgery mean scores were significantly lower in the rectal group compared to the IV group (IV group 2.33; rectal group 1.7; P=0.019 - **significant**). Emergence agitation/Patient's Condition Upon Arrival at Recovery Four-point score: 1- Quiet child (no need for intervention), 2– A child that	**Limitations include:** • Small sample (96) • Not all statistics reported for time to first analgesia ***Author's Conclusions:*** Altogether, according to the results obtained from this study, rate of post-adenotonsillectomy pain in 4th and 6th hours after the surgery in rectal acetaminophen group was less than that in the IV group, and the time for consumption the first additional painkiller in rectal group was delayed. Also, the need for postoperative additional analgesic medication in the rectal acetaminophen group was evidently less than that in IV acetaminophen group. ***Risk of Bias*** ***Random Sequence Generation (Selection Bias)***: "The simple randomization was done through selection of either A (for IV acetaminophen) or B (for rectal acetaminophen) card by each patient"– **Unclear Risk** ***Allocation Concealment (Selection Bias)***: "The simple randomization was done through selection of either A (for IV acetaminophen) or B (for rectal acetaminophen) card by each patient" – **Low Risk** ***Blinding of Participants and Personnel (Performance Bias)***: " The study was organized in a double-blinded design (i.e. neither the patient nor the assessor knew about the administered medication); however, only the prescribing person was aware of the prescribed drug in order to take required measures in case of unfavorable medication complication" - **Low Risk**

Citation	Study design	Population (n)	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
				could be comforted (requiring physical contact with parents), 3- Restless child (crying), 4- Child in aggressive mode (requiring physical control to prevent harming themselves). • No significant difference found between groups (P = 0.207 – **not significant**	***Blinding of Outcome Assessment (Detection Bias)***: As above - Low Risk ***Incomplete Outcome Data (Attrition Bias)***: All completed - - Low Risk ***Selection Reporting (Reporting Bias)***: Not all statistics reported - Unclear Risk ***Other Bias***: No other detected - Low Risk

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
Khalili et al (2016) (1)	Randomized, double-blind, prospective, placebo controlled	N=120; aged 6months – 6 years; scheduled for elective surgical repair of unilateral inguinal hernia Patient Characteristics: No statistically significance difference across all groups	**Intravenous paracetamol versus rectal paracetamol** 1) *Preoperatively (after induction) - intravenous paracetamol, 15mg/kg* *OR* 2) *Preoperatively (after induction) - rectal paracetamol 40mg/kg* OR 3) *Preoperatively (after induction) - intravenous placebo* *OR* 4) *Preoperatively (after induction) rectal placebo* Rescue analgesia rectal paracetamol 40mg/kg	**Primary outcome of postoperative pain** Postoperative Pain – Pain intensity Based on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale • Significant differences between the intervention (paracetamol IV and paracetamol rectal) groups' mean scores of pain compared to placebo groups immediately (P<0.001), 30 minutes (P<0.001), 1 hour (P>0.001), and 2 hours after extubation (P= 0.01) **- significant**. • No significant differences between intervention and placebo groups were observed at 4, 6, and 12 hours after extubation (P = 0.43, 0.57, & 0.22, respectively – **not significant**). • Mean differences of IV paracetamol group were lower than rectal paracetamol group at all time intervals however these were not significantly different **– not significant**. Additional Analgesics • Significant difference in the mean frequency of receiving additional analgesics between paracetamol groups and placebo (P = 0.02) – No difference between paracetamol groups reported - **further details not reported.** Postoperative Vomiting • difference between paracetamol groups was not significantly different – **not significant but figure not reported**. Sedation Levels Richmond Agitation-Sedation Scale (RASS) • Mean sedation levels were significantly higher the placebo groups compared to the intervention paracetamol groups (IV paracetamol 0, rectal paracetamol 1, placebo groups 2; P = 0.02 – **significant**) Length of stay in the recovery room Modified Aldrete Score	Limitations include: • Small sample (120) • Not all statistics reported ***Authors Conclusions:*** Results confirmed both forms of the medicine to have significantly higher analgesic effects compared to placebo. Greatest analgesic effect during the first hour after surgery was observed in the IV paracetamol group, both forms of acetaminophen had similar & acceptable efficacy in pain relief two hours after surgery ***Risk of Bias*** ***Random Sequence Generation (Selection Bias)***: Randomisation but method not described – Unclear Risk ***Allocation Concealment (Selection Bias)***: Not described – Unclear Risk ***Blinding of Participants and Personnel (Performance Bias)***: After induction- Low Risk ***Blinding of Outcome Assessment (Detection Bias)***: A trained staff member who was unaware of the administered medicines recorded pain scores, sedation levels, frequency of vomiting, length of stay in the recovery room, and duration of operation in a questionnaire. – Low Risk ***Incomplete Outcome Data (Attrition Bias)***: All completed – Low Risk ***Selection Reporting (Reporting Bias)***: Not all statistics reported - Unclear Risk

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Risk of Bias and Comments
				• No significant difference between paracetamol intervention groups and placebo groups in length of stay (IV paracetamol 67 ± 8.7, rectal paracetamol 67.2 ± 13.1, IV placebo 68.3 ± 12.3, rectal placebo 68.5 ± 13.2; P=0.96 – **not significant**).	***Other Bias***: No other detected - **Low Risk**

Clinical Practice Guidelines

An international guideline was identified for postoperative pain management in children developed by the Pain committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative) (17). The recommendations in the guideline were categorised by procedure. The AGREE II checklist tool was applied to the guideline and assessed by two reviewers. The guidelines were considered not be of good quality with an overall score of less than 50% and a very low score in the rigour and methodology domain of 13% (See Appendix C).

Two South African clinical practice guidelines were identified that were developed by South African Society Of Anaesthesiologists (SASA); the South African Acute Pain Guidelines 2015 (18) and SASA paediatric guidelines for the safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in children: 2021–2026 (19). Both included paracetamol and provided recommended dosages for all routes of administration but a specific route was not specifically recommended over another.

8. Evidence Quality

All three studies were randomised controlled trials. Each study was evaluated for risk of bias (See Table 2) and outcomes assessed with GRADE (See Summary of Findings Table). Risk of bias was considered serious or very serious in the three included RCTs as statistics on included outcomes were not fully reported. Furthermore, methods for randomisation and concealment were not fully described. All three RCTs included had very small sample sizes resulting in downgrading for serious imprecision. Meta-analysis was not conducted on outcomes where there more than one study however many results for outcomes were contrasting. Population and settings for studies were quite different however it could not be determined for certain if this could explain the difference in results. Overall certainty in the evidence was assessed to be very low.

9. Alternative agents

Paracetamol suppositories

10. Cost Comparison

A cost comparison was conducted utilising rectal dosage per the Paediatric Hospital Level STGs and the South African Society Of Anaesthesiologists (SASA) guidelines (40mg/kg then 30mg/kg thereafter), and IV dosage as per the professional information and SASA guidelines (15mg/kg 6 hourly), assuming no sharing of IV paracetamol vials.

Table 4: Costing

Dosage Form	IV		RECTAL		DIFFERENCE IV vs Rectal	
Child kg	*Cost per day per child~*	*Est. contract price**	*Cost per day per child***	*Est. contract price **	*Cost per day per child~***	*Est. contract price**
10	R33,28	R20,97	R37,99	R23,93	R4,71	R2,97
15	R33,28	R20,97	R58,45	R36,82	R25,17	R15,86

Costs were based on the most appropriate formulation size and lowest cost option.

~SEP December 2021 – Fresenius 50ml 10mg IV paracetamol

*Based on price reduction achieved on 100ml IV paracetamol = 63% of SEP, 33% discount

** SEP December 2021 – Empaped125mg/250mg suppositories

Cost of IV paracetamol is estimated to be less than rectal paracetamol – cost savings of R2.97 and R15.86 for a 10kg and 15kg child respectively (est. contract price).

11 Discussion and Conclusion

Overall, the quality of evidence was very low with small sample sizes in most trials, inconsistency between results and serious or very serious risk of bias. The evidence did not indicate superiority of rectal or IV paracetamol in terms of pain intensity, time to first analgesia dose post-operatively, overall need for analgesia in recovery room as well as after the recovery room. The evidence did not reveal significant adverse events or safety concerns related to rectal or IV routes. However, pharmacokinetic studies indicate that the pharmacokinetics of paracetamol following rectal administration are highly variable and unpredictable (varying 25-100%)(20–22). Paracetamol suppositories cannot be administered to children under 3 months whereas IV paracetamol can be safely. Rectal paracetamol is more expensive than IV paracetamol. In the setting where paracetamol is required but the oral route is not available, IV paracetamol is a suitable option. It is thus proposed that IV paracetamol be included as an alternative to oral paracetamol when the oral route is not possible. Risk of indication creep is acknowledged. Theatre is a controlled environment where this intervention can be managed and monitored. This will aid in prevention of irrational use outside of this setting and indication creep.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Intravenous compared to rectal paracetamol* - Very low quality evidence - 3 RCTs (n=262) ages 6 months to 10 years See Summary of Findings Table
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	***Pain intensity 4 hours after extubation*** - Haddadi et al. 2014, RCT, n=96, mean difference 0.71 (in favour of rectal) 95% CI [0.26 – 1.16], P=0.003. - Khalili et al, 2016, RCT, n=120, no difference found. ***Pain intensity 6 hours after extubation*** - Haddadi et al. 2014, RCT, n=96, mean difference 0.63 (in favour of rectal) 95% CI [0.12 – 1.14], p=0.019. - Khalili et al. 2016, RCT, n=120, mean difference 0.2 (in favour of IV), reported as not significant). ***Time to first analgesia after surgery*** - Capici et al. 2008, RCT, n=46, median difference 3 hours (in favour of rectal), p=0.01. - Khalili et al. 2016, RCT, n=120, mean difference 1.15 hours (in favour of rectal), p value not reported). ***Number of children requiring analgesia after the recovery room*** - Capici et al. 2008, RCT, n=46 (22 out 23 in rectal vs 23 out 23 in IV), p value not reported; - Haddadi et al, 2014, n=96, p=0.0001 in favour of rectal, numbers not reported.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [ ] Very low: [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*See Summary of findings table*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [X]	No significant events reported for any dosage forms
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [ ] Favours control: [ ] Intervention = Control *or* Uncertain: [X]	No difference in adverse events between routes however there is varying bioavailability of rectal.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	Theatre is a controlled environment where this intervention can be managed and monitored. This will also prevent the irrational use outside of this indicate, and indication creep.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [X] Uncertain: [ ]	**Less intensive or IV compared to rectal paracetamol** 10kg child cost savings on SEP p/day =R4,71 10kg child cost savings on est. contract price p/day =R2,97 15kg child cost savings on SEP p/day = R25,17 15kg child cost savings on est. contract price p/day=R15,86

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	No specific data on acceptability have been accessed. However, there are cultural differences in relation to the acceptability of the rectal route.
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[X]	[ ]

Recommendation

The Paediatric Hospital Level Expert Review Committee suggests adding intravenous paracetamol, to the Essential Medicines List for peri-operative pain in paediatric patients, as an alternative to rectal paracetamol, when the oral route of administration is not possible.

Rationale:

Although the evidence was very limited, IV paracetamol was not shown to be inferior to rectal paracetamol and no safety concerns were found. Furthermore, IV paracetamol can be utilised safely in children under 3 months whereas rectal cannot. The cost of IV paracetamol is predicted to be less than that of rectal paracetamol which is currently not on tender.

Level of Evidence:

Small trials with outcomes of very low quality

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	X

VEN status:

Vital	Essential	Necessary
[ ]	X	[ ]

Monitoring and evaluation considerations

Research priorities

References

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2. Alhashemi JA, Daghistani MF. Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. Eur J Anaesthesiol. 2007 Feb;24(2):128–33.

3. Alhashemi JA, Daghistani MF. Effects of intraoperative i.v. acetaminophen vs i.m. meperidine on post-tonsillectomy pain in children. Br J Anaesth. 2006 Jun;96(6):790–5.

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6. Aksoy M, İnce İ, Ahıskalıoğlu A, Keleş S, Doymuş Ö. Effect of intravenous preoperative versus postoperative paracetamol on postoperative nausea and vomiting in patients undergoing strabismus surgery: A prospective randomized study. Agri Agri Algoloji Derneginin Yayin Organidir J Turk Soc Algol. 2018 Jan;30(1):1–7.

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13. Fearon JA, Dimas V, Ditthakasem K, Herbert MA. A Randomized Controlled Trial of Oral Versus Intravenous Administration of a Nonnarcotic Analgesia Protocol Following Pediatric Craniosynostosis Corrections on Nausea and Vomiting Rates. J Craniofac Surg. 2015 Sep;26(6):1951–3.

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19. SASA paediatric guidelines for the safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in children: 2021–2026. South Afr J Anaesth Analg [Internet]. 2021 Jan [cited 2022 Feb 25];27(4). Available from: http://journals.co.za/doi/10.36303/SAJAA.2021.27.4.S2.2635

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Appendix A

Database: PubMed
Date: January 2022

Search	Query	Results
#1	Search: ((((("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("acetaminophen"[MeSH Terms] OR "acetaminophen"[All Fields] OR "paracetamol"[All Fields] OR "acetaminophen s"[All Fields] OR "acetaminophene"[All Fields] OR "acetaminophens"[All Fields] OR "paracetamol s"[All Fields] OR "paracetamols"[All Fields])) OR ("IV"[All Fields] AND ("acetaminophen"[MeSH Terms] OR "acetaminophen"[All Fields] OR "paracetamol"[All Fields] OR "acetaminophen s"[All Fields] OR "acetaminophene"[All Fields] OR "acetaminophens"[All Fields] OR "paracetamol s"[All Fields] OR "paracetamols"[All Fields]))) OR (("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("acetaminophen"[MeSH Terms] OR "acetaminophen"[All Fields] OR "paracetamol"[All Fields] OR "acetaminophen s"[All Fields] OR "acetaminophene"[All Fields] OR "acetaminophens"[All Fields] OR "paracetamol s"[All Fields] OR "paracetamols"[All Fields]))) AND ("IV"[All Fields] AND ("acetaminophen"[MeSH Terms] OR "acetaminophen"[All Fields] OR "paracetamol"[All Fields] OR "acetaminophen s"[All Fields] OR "acetaminophene"[All Fields] OR "acetaminophens"[All Fields] OR "paracetamol s"[All Fields] OR "paracetamols"[All Fields])) AND ("pain, postoperative"[MeSH Terms] OR ("pain"[All Fields] AND "postoperative"[All Fields]) OR "postoperative pain"[All Fields] OR ("postoperative"[All Fields] AND "pain"[All Fields]))) AND ((y_10[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (english[Filter]))	142
#2	Search: (("intravenous"[Title/Abstract] OR "intravenously"[Title/Abstract] OR "IV"[Title/Abstract]) AND ("paracetamol"[Title/Abstract] OR "acetaminophen"[Title/Abstract]) AND ("postoperative"[Title/Abstract] OR "post-operative"[Title/Abstract]) AND ("pain"[Title/Abstract] OR "analgesia"[Title/Abstract]) AND (children[MeSH Terms])) ("intravenous"[Title/Abstract] OR "intravenously"[Title/Abstract] OR "IV"[Title/Abstract]) AND ("paracetamol"[Title/Abstract] OR "acetaminophen"[Title/Abstract]) AND ("postoperative"[Title/Abstract] OR "post-operative"[Title/Abstract]) AND ("pain"[Title/Abstract] OR "analgesia"[Title/Abstract]) AND "child"[MeSH Terms] Translations children[MeSH Terms]: "child"[MeSH Terms]	148
#3	(("intravenous"[Title/Abstract] OR "intravenously"[Title/Abstract] OR "IV"[Title/Abstract]) AND ("paracetamol"[Title/Abstract] OR "acetaminophen"[Title/Abstract]) AND ("postoperative"[Title/Abstract] OR "post-operative"[Title/Abstract]) AND ("pain"[Title/Abstract] OR "analgesia"[Title/Abstract]) AND (children[MeSH Terms])) Filters: English, from 1000/1/1 - 2022/1/31 Sort by: Most Recent (("intravenous"[Title/Abstract] OR "intravenously"[Title/Abstract] OR "IV"[Title/Abstract]) AND ("paracetamol"[Title/Abstract] OR "acetaminophen"[Title/Abstract]) AND ("postoperative"[Title/Abstract] OR "post-operative"[Title/Abstract]) AND ("pain"[Title/Abstract] OR "analgesia"[Title/Abstract]) AND "child"[MeSH Terms]) AND ((1000/1/1:2022/1/31[pdat]) AND (english[Filter])) Translations children[MeSH Terms]: "child"[MeSH Terms]	138

Database: Cochrane Library
Date: January 2022

ID	Search	Hits
#1	MeSH descriptor: [Administration, Intravenous] explode all trees	19183
#2	MeSH descriptor: [Acetaminophen] explode all trees	3436
#3	MeSH descriptor: [Pain, Postoperative] explode all trees	16869
#4	MeSH descriptor: [Child] explode all trees	60484
#5	#1 AND #2 AND #3 AND #4 in Cochrane Reviews	1

Database: Epistemonikos Database
Date: February 2022

Full query: (title:((title:(intravenous OR intravenously OR IV) OR abstract:(intravenous OR intravenously OR IV)) AND (title:(paracetamol OR acetaminophen) OR abstract:(paracetamol OR acetaminophen)) AND (title:(post-operative OR postoperative OR post operative) OR abstract:(post-operative OR postoperative OR post operative)) AND (title:(pain OR analgesia) OR abstract:(pain OR analgesia)) AND (title:(child OR children OR adolescent OR paediatric) OR abstract:(child OR children OR adolescent OR paediatric))) OR abstract:((title:(intravenous OR intravenously OR IV) OR abstract:(intravenous OR intravenously OR IV)) AND (title:(paracetamol OR acetaminophen) OR abstract:(paracetamol OR acetaminophen)) AND (title:(post-operative OR postoperative OR post operative) OR abstract:(post-operative OR postoperative OR post operative)) AND (title:(pain OR analgesia) OR abstract:(pain OR analgesia)) AND (title:(child OR children OR adolescent OR paediatric) OR abstract:(child OR children OR adolescent OR paediatric))))

Results = 2

Appendix B List of Excluded Studies with Reasons

Full Reference	Reason for Exclusion
Aksoy M, İnce İ, Ahıskalıoğlu A, Keleş S, Doymuş Ö. Effect of intravenous preoperative versus postoperative paracetamol on postoperative nausea and vomiting in patients undergoing strabismus surgery: A prospective randomized study. Agri. 2018 Jan;30(1):1-7. doi: 10.5505/agri.2017.65872. PMID: 29450877.	Wrong comparator
Aldamluji N, Burgess A, Pogatzki-Zahn E, Raeder J, Beloeil H; PROSPECT Working Group collaborators*. PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2021 Jul;76(7):947-961. doi: 10.1111/anae.15299. Epub 2020 Nov 17. PMID: 33201518; PMCID: PMC8247026.	Only one study included in review that matches PICO, so study sourced and included instead
Alhashemi JA, Daghistani MF. Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. Eur J Anaesthesiol. 2007 Feb;24(2):128-33. doi: 10.1017/S0265021506001232. Epub 2006 Aug 8. PMID: 16895621.	Wrong comparator – paracetamol IV versus another agent
Allen AH. Is i.v. access necessary for myringotomy with tubes? Ear Nose Throat J. 2007 Nov;86(11):672-4, 681. PMID: 18225626.	Incorrect study design
Alohali AA, Al-Rubaian N, Tatsi C, Sood S, Hosey MT. Post-operative pain and morbidity in children who have tooth extractions under general anaesthesia: a service evaluation. Br Dent J. 2019 Oct;227(8):713-718. doi: 10.1038/s41415-019-0807-4. PMID: 31654008.	Wrong comparator – paracetamol IV versus another agent
Boric K, Dosenovic S, Jelicic Kadic A, Batinic M, Cavar M, Urlic M, Markovina N, Puljak L. Interventions for postoperative pain in children: An overview of systematic reviews. Paediatr Anaesth. 2017 Sep;27(9):893-904. doi: 10.1111/pan.13203. Epub 2017 Jul 14. PMID: 28707454.	Studies included in review do not match PICO
Ceelie I, de Wildt SN, van Dijk M, van den Berg MM, van den Bosch GE, Duivenvoorden HJ, de Leeuw TG, Mathôt R, Knibbe CA, Tibboel D. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. JAMA. 2013 Jan 9;309(2):149-54. doi: 10.1001/jama.2012.148050. PMID: 23299606.	Wrong comparator – paracetamol IV versus another agent
Chidambaran V, Subramanyam R, Ding L, Sadhasivam S, Geisler K, Stubbeman B, Sturm P, Jain V, Eckman MH. Cost-effectiveness of intravenous acetaminophen and ketorolac in adolescents undergoing idiopathic scoliosis surgery. Paediatr Anaesth. 2018 Mar;28(3):237-248. doi: 10.1111/pan.13329. Epub 2018 Jan 29. PMID: 29377376; PMCID: PMC6004284.	Wrong comparator and incorrect study design
Chisholm AG, Sathyamoorthy M, Seals SR, Carron JD. Does intravenous acetaminophen reduce perioperative opioid use in pediatric tonsillectomy? Am J Otolaryngol. 2019 Nov-Dec;40(6):102294. doi: 10.1016/j.amjoto.2019.102294. Epub 2019 Sep 9. PMID: 31521403.	Incorrect study design
Courrèges P. Inadvertent epidural infusion of paracetamol in a child. Paediatr Anaesth. 2005 Dec;15(12):1128-30. doi: 10.1111/j.1460-9592.2005.01584.x. PMID: 16324038.	Incorrect route of administration
Dashti GA, Amini S, Zanguee E. The prophylactic effect of rectal acetaminophen on postoperative pain and opioid requirements after adenotonsillectomy in children. Middle East J Anaesthesiol. 2009 Jun;20(2):245-9. PMID: 19583073.	Wrong intervention and comparator
Fearon JA, Dimas V, Ditthakasem K, Herbert MA. A Randomized Controlled Trial of Oral Versus Intravenous Administration of a Nonnarcotic Analgesia Protocol Following Pediatric Craniosynostosis Corrections on Nausea and Vomiting Rates. J Craniofac Surg. 2015 Sep;26(6):1951–3	Wrong comparator
Grabski DF, Vavolizza RD, Roecker Z, Levin D, Swanson JR, McGahren ED, Gander JW. Reduction of post-operative opioid use in neonates following open congenital diaphragmatic hernia repairs: A quality improvement initiative. J Pediatr Surg. 2022 Jan;57(1):45-51. doi: 10.1016/j.jpedsurg.2021.09.027. Epub 2021 Sep 20. PMID: 34686379.	Incorrect study design
Haliloglu AH, Gokce MI, Tangal S, Boga MS, Tapar H, Aladag E. Comparison of postoperative analgesic efficacy of penile block, caudal block and intravenous paracetamol for circumcision: a prospective randomized study. Int Braz J Urol. 2013 Jul-Aug;39(4):551-7. doi: 10.1590/S1677-5538.IBJU.2013.04.13. PMID: 24054383.	Wrong comparator – paracetamol IV versus another agent
Hiller, Arja PhD, MD*; Helenius, Ilkka PhD, MD†; Nurmi, Elisa MD*; Neuvonen, Pertti J. PhD, MD‡; Kaukonen, Maija PhD, MD§; Hartikainen, Tuula RN*; Korpela, Reijo MD*; Taivainen, Tomi PhD, MD*; Meretoja, Olli A. MD* Acetaminophen Improves Analgesia but Does Not Reduce Opioid Requirement After Major Spine Surgery in Children and Adolescents, Spine: September 15, 2012 - Volume 37 - Issue 20 - p E1225-E1231 doi: 10.1097/BRS.0b013e318263165c	Wrong comparator - placebo
Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. Anesthesiology. 2010 Sep;113(3):672-7. doi: 10.1097/ALN.0b013e3181e2c34b. PMID: 20693884.	Wrong comparator – paracetamol IV versus another agent
Iodice FG, Thomas M, Walker I, Garside V, Elliott MJ. Analgesia in fast-track paediatric cardiac patients. Eur J Cardiothorac Surg. 2011 Sep;40(3):610-3. doi: 10.1016/j.ejcts.2010.12.032. Epub 2011 Feb 20. PMID: 21342774.	Incorrect study design
Jahr JS, Lee VK. Intravenous acetaminophen. Anesthesiol Clin. 2010 Dec;28(4):619-45. doi: 10.1016/j.anclin.2010.08.006. PMID: 21074742.	Incorrect study design
Keles S, Kocaturk O, Demir P. Efficacy of Preemptive Analgesia on Postoperative Pain Control in Children Who Underwent Full-Mouth Dental Rehabilitation Under General Anesthesia: A Randomized Controlled Clinical Trial. J Oral Facial Pain Headache. 2021 Fall;34(4):297-302. doi: 10.11607/ofph.2960. PMID: 34990498.	Wrong comparator
Kharouba J, Hawash N, Peretz B, Blumer S, Srour Y, Nassar M, Sabbah M, Safadi A, Khorev A, Somri M. Effect of intravenous paracetamol as pre-emptive compared to preventive analgesia in a pediatric dental setting: a prospective randomized study. Int J Paediatr Dent. 2018 Jan;28(1):83-91. doi: 10.1111/ipd.12311. Epub 2017 Jun 15. PMID: 28618198.	Wrong comparator
Kocum AI, Sener M, Caliskan E, Bozdogan N, Micozkadioglu D, Yilmaz I, Aribogan A. Intravenous paracetamol and dipyrone for postoperative analgesia after day-case tonsillectomy in children: a prospective, randomized, double blind, placebo controlled study. Braz J Otorhinolaryngol. 2013 Jan-Feb;79(1):89-94. English, Portuguese. doi: 10.5935/1808-8694.20130015. PMID: 23503913.	Wrong comparator – paracetamol IV versus another agent

Full Reference	Reason for Exclusion
Aksoy M, İnce İ, Ahıskalıoğlu A, Keleş S, Doymuş Ö. Effect of intravenous preoperative versus postoperative paracetamol on postoperative nausea and vomiting in patients undergoing strabismus surgery: A prospective randomized study. Agri. 2018 Jan;30(1):1-7. doi: 10.5505/agri.2017.65872. PMID: 29450877.	Wrong comparator
Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. Anesthesiology. 1999 Aug;91(2):442-7. doi: 10.1097/00000542-199908000-00019. PMID: 10443608.	Only one study included in review that matches PICO, so study sourced and included instead
Lammers CR, Schwinghammer AJ, Hall B, Kriss RS, Aizenberg DA, Funamura JL, et al. Comparison of Oral Loading Dose to Intravenous Acetaminophen in Children for Analgesia After Tonsillectomy and Adenoidectomy: A Randomized Clinical Trial. Anesth Analg. 2021 Dec 1;133(6):1568–76	Wrong comparator
Mann GE, Flamer SZ, Nair S, Maher JN, Cowan B, Streiff A, Adams D, Shaparin N. Opioid-free anesthesia for adenotonsillectomy in children. Int J Pediatr Otorhinolaryngol. 2021 Jan;140:110501. doi: 10.1016/j.ijporl.2020.110501. Epub 2020 Nov 27. PMID: 33290925.	Wrong comparator and incorrect study design
McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. Cochrane Database Syst Rev. 2016 May 23;2016(5):CD007126. doi: 10.1002/14651858.CD007126.pub3. PMID: 27213715; PMCID: PMC6353081.	Only one study included in review that matches PICO, so study sourced and included instead
Mian P, Valkenburg AJ, Allegaert K, Koch BCP, Breatnach CV, Knibbe CAJ, Tibboel D, Krekels EHJ. Population Pharmacokinetic Modeling of Acetaminophen and Metabolites in Children After Cardiac Surgery With Cardiopulmonary Bypass. J Clin Pharmacol. 2019 Jun;59(6):847-855. doi: 10.1002/jcph.1373. Epub 2019 Jan 11. PMID: 30633373; PMCID: PMC6590134.	Incorrect study design
Mitchell RB, Archer SM, Ishman SL, Rosenfeld RM, Coles S, Finestone SA, Friedman NR, Giordano T, Hildrew DM, Kim TW, Lloyd RM, Parikh SR, Shulman ST, Walner DL, Walsh SA, Nnacheta LC. Clinical Practice Guideline: Tonsillectomy in Children (Update). Otolaryngol Head Neck Surg. 2019 Feb;160(1_suppl):S1-S42. doi: 10.1177/0194599818801757. PMID: 30798778.	Guideline – route not specified
Murat I, Baujard C, Foussat C, Guyot E, Petel H, Rod B, Ricard C. Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. Paediatr Anaesth. 2005 Aug;15(8):663-70. doi: 10.1111/j.1460-9592.2004.01518.x. PMID: 16029401.	Wrong comparator – paracetamol IV versus another agent
Nikooseresht M, Nasrolahi M, Hajian P, Moradi A. The Effects of Ondansetron on the Analgesic Action of Intravenous Acetaminophen after Tonsillectomy in Children: A Triple-Blind Randomized Controlled Trial. Oxid Med Cell Longev. 2021 Apr 23;2021:6611740. doi: 10.1155/2021/6611740. PMID: 33981386; PMCID: PMC8088369.	Wrong intervention
Nour C, Ratsiu J, Singh N, Mason L, Ray A, Martin M, et al. Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children: a randomized placebo controlled trial. Paediatr Anaesth. 2014 Jun;24(6):574–81	Wrong comparator
Pendeville PE, Von Montigny S, Dort JP, Veyckemans F. Double-blind randomized study of tramadol vs. paracetamol in analgesia after day-case tonsillectomy in children. Eur J Anaesthesiol. 2000 Sep;17(9):576-82. doi: 10.1046/j.1365-2346.2000.00729.x. PMID: 11029125.	Wrong comparator – paracetamol IV versus another agent
Roberts CA, Shah-Becker S, O'Connell Ferster A, Baker A, Stahl LE, Sedeek K, Carr MM. Randomized Prospective Evaluation of Intraoperative Intravenous Acetaminophen in Pediatric Adenotonsillectomy. Otolaryngol Head Neck Surg. 2018 Feb;158(2):368-374. doi: 10.1177/0194599817728911. Epub 2017 Sep 5. PMID: 28873028.	Wrong comparator – adjuvant IV
Rugytė D, Gudaitytė J. Intravenous Paracetamol in Adjunct to Intravenous Ketoprofen for Postoperative Pain in Children Undergoing General Surgery: A Double-Blinded Randomized Study. Medicina (Kaunas). 2019 Apr 1;55(4):86. doi: 10.3390/medicina55040086. PMID: 30939851; PMCID: PMC6524359.	Wrong comparator – paracetamol IV versus another agent
Sener M, Kocum A, Caliskan E, Yilmaz I, Caylakli F, Aribogan A. Administration of paracetamol versus dipyrone by intravenous patient-controlled analgesia for postoperative pain relief in children after tonsillectomy. Braz J Anesthesiol. 2015 Nov-Dec;65(6):476-82. doi: 10.1016/j.bjane.2013.09.010. Epub 2013 Oct 29. PMID: 26614145.	Wrong comparator – paracetamol IV versus another agent
Sola R Jr, Desai AA, Gonzalez KW, Doyle NM, Weaver KL, Poola AS, Fraser JD, St Peter SD, Millspaugh DL. Does Intravenous Acetaminophen Improve Postoperative Pain Control after Laparoscopic Appendectomy for Perforated Appendicitis? A Prospective Randomized Trial. Eur J Pediatr Surg. 2019 Apr;29(2):159-165. doi: 10.1055/s-0037-1615276. Epub 2018 Jan 2. PMID: 29294507.	Wrong comparator – paracetamol IV versus another agent
Tzortzopoulou A, McNicol ED, Cepeda MS, Francia MB, Farhat T, Schumann R. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD007126. doi: 10.1002/14651858.CD007126.pub2. Update in: Cochrane Database Syst Rev. 2016;(5):CD007126. PMID: 21975764.	Studies included in review on adults only as studies on children did not meet the review's PICO.
Uysal HY, Takmaz SA, Yaman F, Baltaci B, Başar H. The efficacy of intravenous paracetamol versus tramadol for postoperative analgesia after adenotonsillectomy in children. J Clin Anesth. 2011 Feb;23(1):53-7. doi: 10.1016/j.jclinane.2010.07.001. PMID: 21296248.	Wrong comparator – paracetamol IV versus another agent
Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. Paediatr Anaesth. 2013 Jun;23(6):475-95. doi: 10.1111/pan.12163. Epub 2013 Apr 9. PMID: 23570544; PMCID: PMC4272569.	Only study included in the review that matches PICO already included
Yenigun A, Yilmaz S, Dogan R, Goktas SS, Calim M, Ozturan O. Demonstration of analgesic effect of intranasal ketamine and intranasal fentanyl for postoperative pain after pediatric tonsillectomy. Int J Pediatr Otorhinolaryngol. 2018 Jan;104:182-185. doi: 10.1016/j.ijporl.2017.11.018. Epub 2017 Nov 23. PMID: 29287863.	Wrong intervention and comparator
Zhu A, Benzon HA, Anderson TA. Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. Anesth Analg. 2017 Nov;125(5):1569-1587. doi: 10.1213/ANE.0000000000002434. PMID: 29049110.	Only study included in the review that matches PICO already included

APPENDIX C – AGREE II Appraisal of guidelines

AGREE II assessment scores																							
postoperative pain management in children and were developed by the Pain committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative)																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	6	7	6	1	7	1	2	1	2	2	5	1	1	6	7	7	2	1	1	1	7	3	4
Appraiser 2	5	4	7	5	1	1	1	1	1	1	4	3	1	1	7	7	7	1	1	1	1	4	1	3
Item Total	12	10	14	11	2	8	2	3	2	3	6	8	2	2	13	14	14	3	2	2	2	11	4	7
Domain Total	36			21			28								41			9				15		150
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	83%			42%			**13%**								97%			2%				46%		**47%**

Overall assessment: Guidelines are not recommened for use in this context

Score: (e.g. domain 1)

$$\frac{\text{Maximum possible score = 7 (highest score) x no. of items x no. of appraisers}}{\text{Minumum possible score = 1 (lowest score) x no. of items x no. of appraisers}}$$

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$