Systematic Review

Preemptive Acetaminophen for Postoperative Analgesia in Children Undergoing Surgery: A Systematic Review and Meta-Analysis

Xin-yi Hua, MMed, Ru-yi Zhang, PhD, Hua Xie, MMed, Zhong-xian Zhu, MMed, and Wei-bing Tang, PhD

From: Department of Pediatric Surgery, Children's Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China

Address Correspondence: Weibing Tang, PhD Department of Pediatric Surgery, Children's Hospital of Nanjing Medical University, 72 Guangzhou Road, Nanjing, 210000, Jiangsu Province, China E-mail: twbcn@njmu.edu.cn

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Background: Preemptive analgesia is an antinociceptive intervention aimed at inhibiting hyperexcitability in both the peripheral and central nervous systems, diminishing the intensity of postoperative pain. Pre-analgesic acetaminophen has been employed extensively in diverse surgical procedures among adult individuals; however, its efficacy in pediatric patients remains controversial.

Objectives: This review aimed to evaluate the impact of preemptive acetaminophen on postoperative pain, rescue analgesia, and nausea and vomiting in children.

Study Design: A meta-analysis of randomized controlled trials (RCTs).

Setting: The electronic databases of PubMed, EMBASE, Cochrane Library, Web of Science, and Sino-Med were searched. The protocol was previously registered in the PROSPERO database under the registration number CRD 42023469972.

Methods: We adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Thirteen RCTs examining the effects of preemptive APAP in pediatrics were incorporated. The risk of bias for each included study was independently assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. A systematic review and meta-analysis were performed using Review Manager Software version 5.4.

Results: A total of 13 studies, observing 718 patients, were included. Our research found that children who received preoperative acetaminophen had a reduction in pain scores within one-2 hours (standardized mean difference [SMD], -2.83; 95% confidence interval [CI], -3.69 to -1.96; $P < 0.001$), and 6-8 hours (SMD,-2.23; 95% CI, -2.84 to -1.61; $P < 0.001$) postoperatively on the VAS scale and a lower incidence of rescue analgesia (odds ratio [OR], 0.50; 95% CI, 0.3-0.82; $P = 0.006$).

Limitations: The main limitation of this meta-analysis is the potential bias in the few studies included.

Conclusion: Preemptive acetaminophen in pediatric patients could effectively alleviate postoperative pain and decrease the need for additional rescue analgesic interventions.

Key words: Acetaminophen, paracetamol, preemptive analgesia, pain management, pediatric surgery, pain score, rescue analgesia, postoperative nausea, vomiting

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Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (1). The increased metabolic activity resulting from postoperative pain might slow down the healing of wounds and hinder the recovery process (2). Additionally, intense postoperative pain has the potential to interfere with brain development in children

(3). Preemptive analgesia, as one of the measures of multimodal analgesia, refers to analgesic intervention induced before the injury-induced stimulus acts on the body (4). By interfering with the creation, transmission, and control of injury-induced signals, the sensitization of peripheral and central pain is blocked, eliminating or further reducing the pain brought by the injury (5). Preemptive analgesia is commonly employed in adult patients undergoing surgical procedures that fall into gynecological (6), orthopedic (7), or ophthalmic (8) categories. Nevertheless, there exists a paucity of research regarding the utilization of preemptive analgesia in pediatric and neonatal populations.

Acetaminophen (also known as paracetamol [APAP]) is commonly utilized for pain relief in pediatric patients because of its established safety profile in clinical practice (9). Previous research has demonstrated that the analgesic effect exerted by acetaminophen occurs through inhibiting the activity of the cyclooxygenase (COX) enzyme in the peripheral system and regulating various pathways in the central system, including the serotonin neurotransmitter decrement pathway, the L-arginine/nitric oxide (NO) pathway, and the endocannabinoid system (10). Currently, preemptive acetaminophen is frequently used in adult surgical procedures. Preoperative oral administration of acetaminophen was effective, convenient, safe, and cost-effective in reducing intraoperative and postoperative pain in phacoemulsification performed using topical anesthesia. In patients undergoing open gynecologic oncology surgery, preemptive acetaminophen significantly diminishes the overall intake of opioids following surgery and decreases the occurrence of postoperative nausea and vomiting (11). However, the effectiveness of acetaminophen remains a potentially contentious debate in children.

Therefore, this systematic review and meta-analysis aimed to evaluate the effects of acetaminophen as a preemptive analgesic in children on postoperative pain, rescue analgesia, and the incidence of nausea and vomiting.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the reporting of meta-analyses of randomized controlled trials (RCTs). The review protocol was preregistered at the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023469972).

Search Strategy

A systematic search was conducted on several databases, including PubMed, EMBASE, Cochrane Library, Web of Science, and Sino-Med. Search terms included: "children," "acetaminophen," "preemptive analgesia," and "randomized controlled trials." The specific search strategy is shown in Table 1. The search was conducted up to April 26, 2024.

Inclusion and Exclusion Criteria

All RCTs examining the effects of preemptive acetaminophen in pediatrics were incorporated in the review. We excluded studies that lacked full-text references, did not include control groups, combined other pharmacological agents, were not limited to pediatric populations, or were not randomized controlled trials.

Data Extraction

Two authors independently evaluated the full manuscripts of all included trials and performed data extraction. Study details (publication year, first author, and country), study design (sample size), characteristics of patients (average age, weight, and type of surgery), administration details (delivery mode, drug dosage, dosing time), and outcome assessment (pain evaluation scales, assessment time, pain scores, rescue analgesia, postoperative nausea and vomiting [PONV]) were extracted (Table 2).

Assessment of Bias

The risk of bias for each included study was independently assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. These included assessments of randomized sequence generation (selection bias), allocation concealment (selection bias), blinding (implementation bias), blinding of outcome assessment (measurement bias), incomplete outcome data (follow-up bias), selective reporting (reporting bias), and other types of bias. There are three evaluation criteria for each item, namely "low risk", "high risk" and "uncertain".

Statistical Analysis

The primary outcome was the postoperative pain score, and the secondary outcomes were the rate of rescue analgesia and the incidence of postoperative nausea and vomiting. Results for pain scores in children are reported as mean ± SD. The incidence of secondary outcomes is reported as OR and its 95% confidence interval (CI). Statistical heterogeneity was assessed us-

ing the I^2 statistic and Cochran's Q statistic. The random effect model was used when significant heterogeneity was observed ($P < 0.05$ or $I^2 > 50\%$). Otherwise, the fixed effect model was used ($P > 0.05$ or $I^2 < 50\%$). Two-tailed probability values < 0.05 were considered statistically significant. All analyses were performed using Review Manager 5.4 software.

Results

Search Results and Study Characteristics

Based on the search strategy, a total of 241 articles were obtained, of which 95 were duplicate research (Fig. 1). After a review of the abstracts, 50 studies were identified as potentially relevant to the research question. Exclusion criteria were the absence of full text (n = 8), the absence of a blank control group (n = 15), research focused on additional medicines used in conjunction with acetaminophen (n = 12), studies involving non-children (n = 1), and non-RCTs (n = 1). Accordingly, the final sample for this analysis comprised 13 RCTs encompassing a sample size of 718 children. Three hundred sixty-nine individuals were administered preemptive acetaminophen, and 349 patients were given a placebo.

Table 1. *Search strategy used in the PubMed database.*

Number	Search Terms
#1	"Child" [Mesh]
#2	"children" [Title/Abstract] OR "pediatric" [Title/Abstract]
#3	#1 OR #2
#4	"Acetaminophen" [Mesh]
#5	"Acetominophen" [Title/Abstract] OR "Hydroxyacetanilide" [Title/Abstract] OR "APAP" [Title/Abstract] OR "p-Acetamidophenol" [Title/Abstract] OR "p-Hydroxyacetanilide" [Title/Abstract] OR "Paracetamol" [Title/Abstract] OR (("n" [All Fields] AND "4-Hydroxyphenyl" [All Fields]) AND "acetanilide" [Title/Abstract]) OR "Acetamidophenol" [Title/Abstract] OR "N-Acetyl-p-aminophenol" [Title/Abstract] OR "Acephen" [Title/Abstract] OR "Acetaco" [Title/Abstract] OR "Tylenol" [Title/Abstract] OR "Anacin-3" [Title/Abstract] OR "Anacin-3" [Title/Abstract] OR "Datril" [Title/Abstract] OR "Panadol" [Title/Abstract] OR "Acamol" [Title/Abstract] OR "Algotropyl" [Title/Abstract]
#6	#4 OR #5
#7	"Preoperative" [Title/Abstract] OR "preemptive" [Title/Abstract]
#8	"Analgesia" [MeSH]
#9	"randomized controlled trial" [Publication Type] OR "randomized" [Title/Abstract] OR "placebo" [Title/Abstract]
#10	#3 AND #6 AND #7 AND #8 AND #9

Literature Quality Evaluation

In the analysis, 61.5% of the studies (8 in total) provided explicit details regarding the methods used to generate a random sequence. Additionally, 54% of the studies (7 in total) described the implementation of allocation concealment. Furthermore, 46% of the studies (6 in total) reported blinding of patients, and one study did not report whether outcome measurement personnel were blinded. In addition, none of the 13 trials provided specific information regarding other potential sources of bias (Fig. 2). No studies were excluded according to the result of this evaluation.

Postoperative Pain Scores

Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) assesses 6 aspects of children's pain: the degree of crying, facial expression, verbal description of pain, body tension, reaction to wound touch, and leg movement (12). Bennie (13) and Mahgoobifard (14) employed the CHEOPS scale (Fig. 3). In Bennie's study, pain assessment was performed at several time intervals following surgery, specifically at 0, 5, 10, 15, 30, 45, and 60 minutes, and the study showed that preanalgesic acetaminophen did not reduce postoperative pain scores. In Mahgoobifard's study, pain assessments were performed upon the children's arrival in the post-anesthesia care unit (PACU) as well as upon their transfer to the ward after one hour. Mahgoobifard's study indicated that the pain score of the experimental group was significantly lower than that of the control group at 0 and 60 min after surgery, a finding inconsistent with the above study.

Visual Analog Scale (VAS) Scale

The Visual Analog Scale (VAS) is a commonly employed instrument for the assessment of subjective pain experiences. This tool consists of a 10 cm ruler (0 = no pain; 10 = maximum intensity). Children are instructed to indicate their perceived pain intensity by selecting a point along the ruler that corresponds to their current level of discomfort (15). Santos (16), Zieliński (17), and Huang (18) all employed the VAS for pain evaluation (Fig. 4). Pain scores were compared between the periods of one-2 hours and 6-8 hours after the operation,

Table 2. *Characteristics of included studies.*

Author, Year	Country	Sample Size		Mean Age		Weight		Delivery Mode	Drug Dosage	Dosing Time	Surgery	Pain Evaluation	Assessment Time	Outcome
		T	C	T	C	T	C							
Bennie, R.E. 1997 (13)	USA	16	14	5.3 ± 4.2	5.2 ± 4.7	20.9 ± 17.0	20.9 ± 14.4	oral	15 mg/kg acetaminophen	30 min before induction	myringotomy	CHEOPS[a]	0, 5, 10, 15, 30, 45, 60 min	pain scores (CHEOPS), behavior scores prior to induction and in the PACUe, duration of anesthesia, oxygen saturation upon arrival to PACU, recovery data, rescue analgesia
Derkay, C.S. 1998 (25)	USA	48	44	29.3 ± 24.6 (mo)	24.1 ± 20.1 (mo)	-	-	oral	10 mg/kg acetaminophen	30-60 min before induction	Bilateral myringotomy with tympanostomy tube placement (BMTT)	Modified Hannallah Objective Pain Scale	0, 15, 30 min	pain scores (Modified Hannallah Objective Pain Scale (1987), length of stay (min), additional pain medication, perioperative vertigo, nausea/vomiting, otorrhea, bleeding, parent's or caregiver's evaluation of his or her child's surgical experience
Anderson, B.J. 2001 (26)	New Zealand	12	30	9.0 ± 3.0	-	37.9 ± 16.6	-	oral	40 mg/kg acetaminophen	30-60 min before induction	tonsillectomy	VAS[b]	hourly intervals after admission to the PACU and continued until discharge from the day-stay facility approximately 4 ± 8 h after surgery	individual acetaminophen serum concentrations and pain scores [VAS 0 ± 10]
		20						oral	100 mg/kg acetaminophen					
Baygin, O. 2011 (27)	Turkey	15	15	9.33 ± 1.397	9.33 ± 2.193	29.33 ± 7.423	30.93 ± 7.778	oral	an age-dosed volume of paracetamol elixir (250 mg/5 mL)	60 min before induction	primary tooth extraction	Five-face scale	at 15 min, one, 2, 3, 4, 5, 6 h, and 24 h after the extraction	self-report pain scores, lip/cheek-biting injury at 24 h after the extraction
Mahgoobifard, Maziar 2014 (14)	Iran	18	21	4-12	-	-	-	oral	15 mg/kg acetaminophen	30 minutes before the operation	adenotonsil-lectomy	CHEOPS	at the time of admission at PACU, 5, 10, 15, 30, 45, and 60 minutes after admission and at discharge from PACU	pain scores (CHEOPS)

Table 2 cont. *Characteristics of included studies.*

Author, Year	Country	Sample Size		Mean Age		Weight		Delivery Mode	Drug Dosage	Dosing Time	Surgery	Pain Evaluation	Assessment Time	Outcome
		T	C	T	C	T	C							
Huang Junwei 2014 (18)	China	30	30	5-14	-	-	-	rectum	40 mg/kg acetaminophen suppository	after general anesthesia	laparoscopic surgery	VAS	One, 4, 8, 16, 24 h after the surgery	The emergence agitation, the Ramsay sedation score, pain scores (VAS) one, 4, 8, 16 and 24 h after operation, adverse effects
Actrn 2018 (28)	Turkey	32	32	9.13 ± 4.24	9.13 ± 3.57	30.50 ± 13.12	28.43 ± 13.41	intravenous	15 mg/kg paracetamol	1h before surgery	strabismus surgery	Faces Pain Scale	every hour starting from when the patients were awake from arrival in the recovery room to 24 h postoperatively	pain scores, complaints of nausea and vomiting, the need for rescue analgesics, and the need for antiemetic drug during 24 h postoperatively
Abou El Fadl, R. 2019 (29)	Egypt	20	20	7.8 ± 0.7	7.6 ± 0.7	-	-	oral	an age-dosed volume (10mL) of acetaminophen (200 mg/5 mL) syrup	1h before starting the treatment	pulpotomy of mandibular primary molars	Modified Wong–Baker FACES Pain Rating Scale (0-3)	before treatment and at the point of unroofing the pulp (during access cavity preparation).	pain scores
Kharouba, J. 2019 (30)	Israel	43	29	8.6 + 2.4	9.8 + 2.2	26.8 ± 7.2	32.7 ± 9.2	oral	15 mg/kg paracetamol	30 minutes prior to dental treatment	tooth extractions	WB[c]	before receiving the preoperative syrup, before treatment, after local anesthesia, after extraction, 4 h and 24 h after the dental treatment	children's self-reported pain-score (Wong–Baker Faces scale), pain behavior scores (MBPS), need for analgesics, children's sensitivity to pain according to parents' assessment, and parents' expectations of their children's cooperation during treatment
Fux-Noy, A. 2020 (20)	Israel	51	51	6.98 ± 1.53	7.08 ± 1.89	-	-	unknown	15 mg/kg paracetamol	15 minutes before dental treatment	dental treatment (filling, pulpotomy, pulpectomy, extraction, SSC, combination)	WB	immediately at the end of the treatment and by phone 2.5 hours after taking the remedy	pain scores (Wong-Baker Facial Rating Pain Scale)

Table 2 cont. *Characteristics of included studies.*

Author, Year	Country	Sample Size		Mean Age		Weight		Delivery Mode	Drug Dosage	Dosing Time	Surgery	Pain Evaluation	Assessment Time	Outcome
		T	C	T	C	T	C							
Santos, P.S. 2020 (16)	Brazil	16	16	7.25 ± 1.34	7.5 ± 1.09	-	-	oral	a weight-dosed volume of paracetamol (200 mg/mL)	1 hour before the local anesthesia	primary molar extraction	VAS	2, 6, and 24 hours after the end of the procedure	trans- and post-operative pain self-reported by the children through a VAS based on a straight line of 100 mm
Raslan, N. 2021 (21)	Syria	22	22	7.54 ± 0.57	7.27 ± 0.71	-	-	oral	10ml acetaminophen syrup (320 mg/10 ml)	30 min before administration of the local anesthetic agent	primary tooth extraction	WB	after injection, after extraction, 15 min, one, 2, 3, 4, 5, and 6 h after extraction	Wong–Baker faces pain-rating scale for pain intensity measurement
Zieliński, J. 2022 (17)	Poland	26	25	6.0 ± 2.7	5.2 ± 2.8	28.0 ± 14.0	23.1 ± 11.1	oral	15 mg/kg acetaminophen	30–45 min before transporting the child to the operating room	otolaryngological procedures (adenoidectomy, adenotonsillotomy, or tonsillectomy)	VAS WB FLACC[d]	One, 2, 4, and 6 h after the surgery	pain scores measured with the VAS, the Wong–Baker Faces Pain Rating Scale (WB), and the Face, Legs, Activity, Cry, and Consolability (FLACC) scale one, 2, 4, and 6 h after surgery

[a]CHEOPS: Children's Hospital of Eastern Ontario Pain Scale; [b]VAS: Visual Analog Scale; [c]WB: Wong–Baker Faces scale; [d]FLACC: Face, Legs, Activity, Crying, Consolability scale; [e]PACU: post-anesthesia care unit

and we found that the pain levels of the 3 clusters in the preoperative acetaminophen group could be considerably lower than those in the control group within one-2 hours after surgery (SMD, -2.83 [95% CI, -3.69 to -1.96; $P < 0.001$]). At 6-8 hours after surgery, the pain scores of the 3 experimental groups were also significantly lower than those of the control group, with SMD -2.23 (95% CI, -2.84 to -1.61; $P < 0.001$).

Wong-Baker (WB) Faces Scale

The Wong-Baker (WB) Faces scale (including 6 categories of facial expressions ranging from 0, a happy smiling face, to 5, a tearful face) is a pain rating scale developed by Donna Wong and Connie Baker (19). Fux-Noy (20), Raslan (21), and Zieliński (17) employed the WB Faces scale to evaluate pain at 2.5 hours, 4 hours, and 4 hours following the surgery, respectively (Fig. 5). In Fux-Noy's study, the control group showed a decreased postoperative pain score, suggesting that administering acetaminophen before surgery did not lower the substantial analgesic. In Raslan and Zieliński's studies, the pain scores of the experimental group were significantly lower than those of the control group. The SMD was -1.09 (95% CI, -2.26 to 0.09; $P < 0.001$). Significant heterogeneity was observed between trials. Therefore, results of the random-effects model are reported.

Rescue Analgesia

Six studies documented the rate of rescue analgesia after surgery (Fig. 6). Given the absence of substantial heterogeneity, a fixed effect model was employed ($I^2 = 0\%$, $P = 0.74$). The incidence of postoperative rescue analgesia was lower in the preemptive acetaminophen group compared to the control group with an odds ratio (OR) of 0.5 (95% CI: 0.3-0.82; $P = 0.006$).

Incidence of Nausea and Vomiting

Six studies reported the incidence of postoperative nausea and vomiting (Fig. 7). No statistically significant heterogeneity was observed in this analysis of PONV; thus, the results of the fixed-effects model are presented (I^2 = 23%, P = 0.26). The prevalence of PONV in the preemptive analgesia group was comparatively higher than that observed in the control group, but the observed difference was not statistically significant (OR=1.59; 95% CI, 0.83 to 3.05; P = 0.16).

Discussion

This systematic review and meta-analysis aimed to evaluate the ability of preemptive acetaminophen to induce postoperative pain relief in children. Our results demonstrated that preoperative acetaminophen can reduce postoperative pain scores and the incidence of postoperative rescue analgesia in pediatric patients. However, preoperative acetaminophen has no substantial impact on the occurrence of postoperative nausea and vomiting.

The utilization of preemptive analgesia with acetaminophen is prevalent in adult populations (22); however, the impact of administering acetaminophen preoperatively on postoperative pain in pediatric patients remains controversial. In this study, a total of 13 RCTs with 718 children were included in the analysis, and different scales were used to assess postoperative pain.

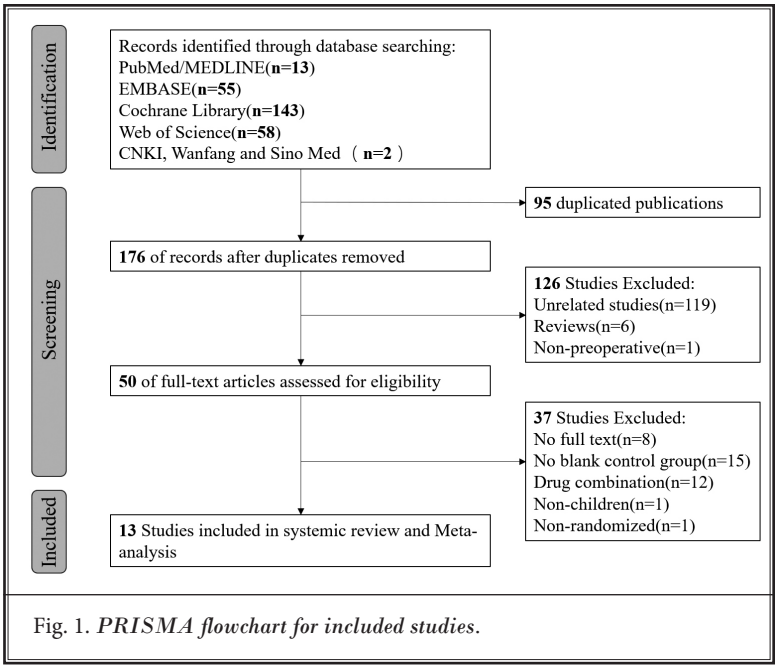

Fig. 1. *PRISMA flowchart for included studies.*

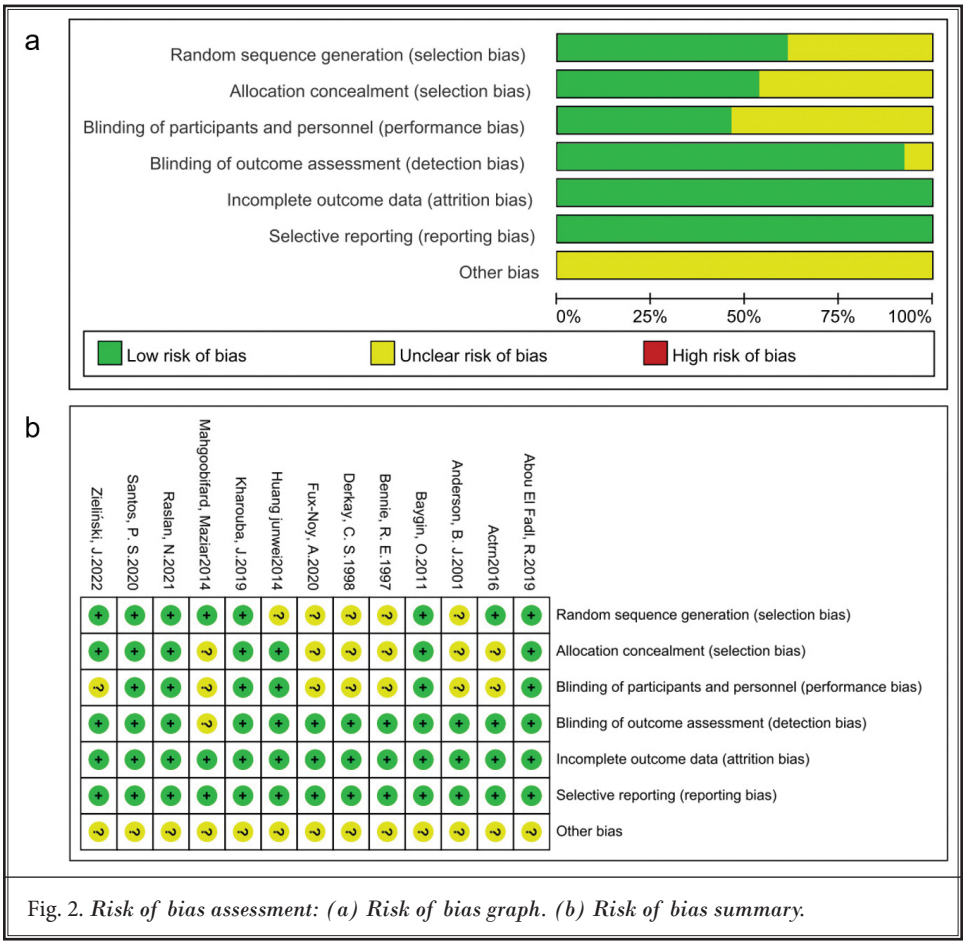

Fig. 2. *Risk of bias assessment: (a) Risk of bias graph. (b) Risk of bias summary.*

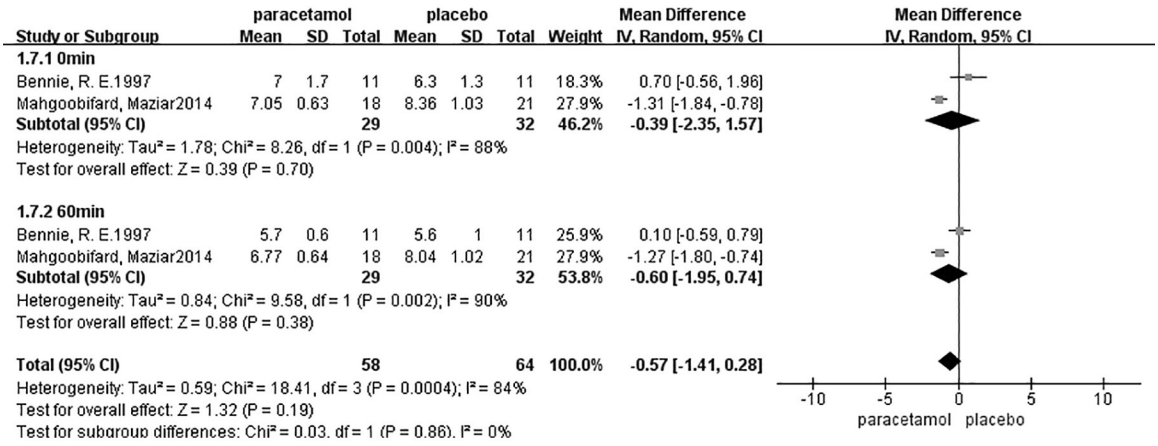

Fig. 3. *Pain scores at 0 and one hour after surgery, according to the CHOPES scale.*

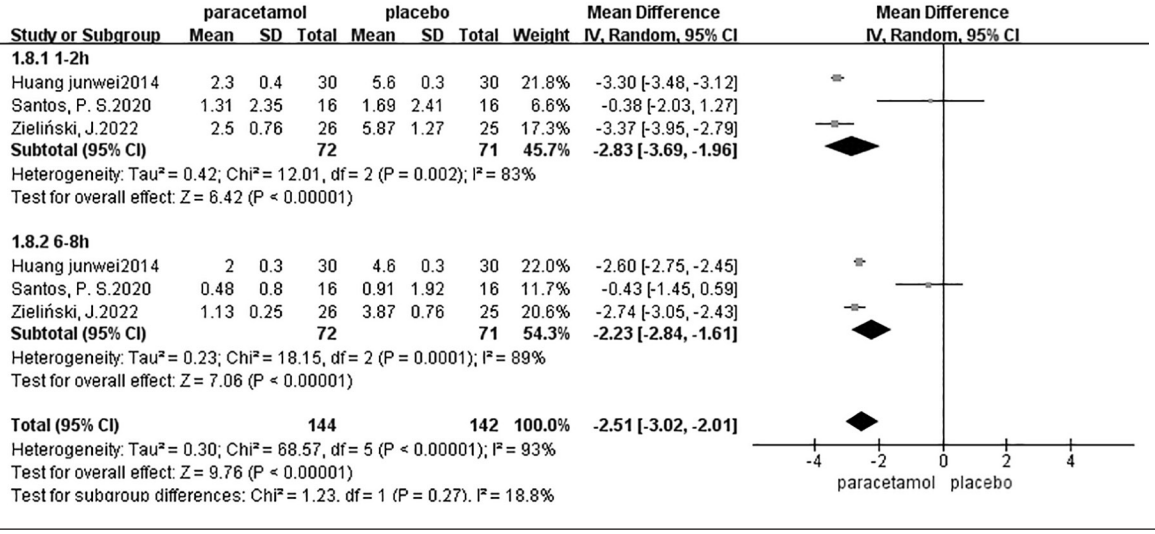

Fig. 4. *Pain scores within one-2 hours and 6-8 hours after surgery, according to the VAS.*

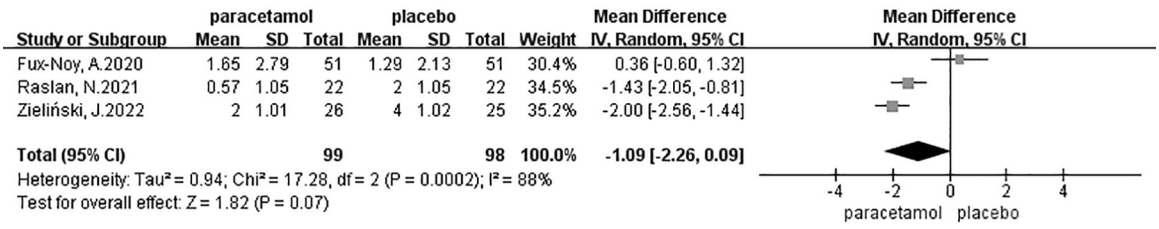

Fig. 5. *Pain scores within 2.5-4 hours after surgery according to the WB scale.*

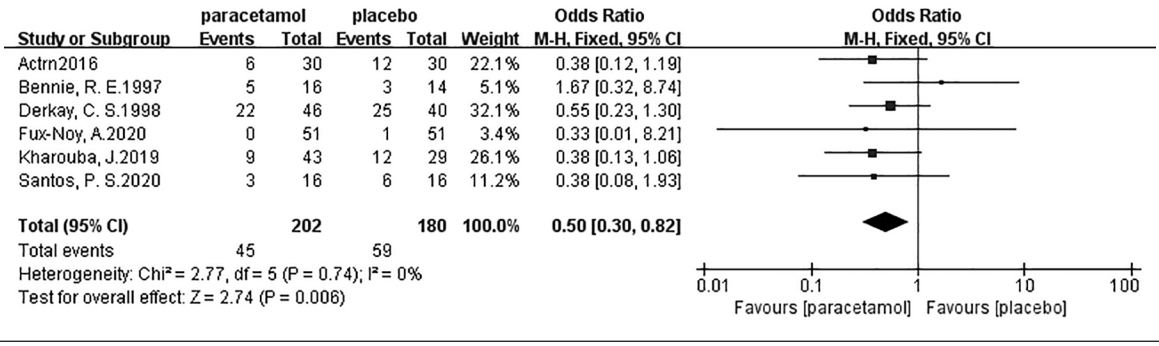

Fig. 6. *The rate of postoperative rescue analgesia.*

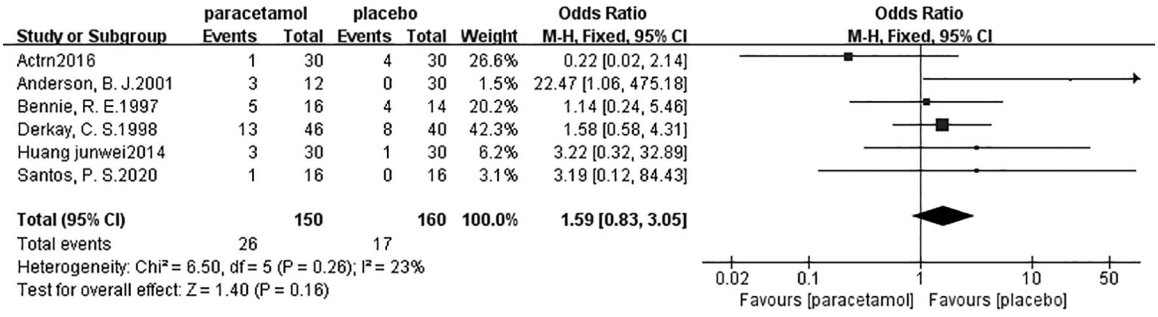

Fig. 7. *The occurrence of postoperative nausea and vomiting.*

Bennie (13) and Mahgoobifard (14) both used the CHEOPS scale to assess pain at 0 hours and one hour after surgery. Mahgoobifard's study indicated that the administration of preoperative acetaminophen analgesia resulted in pain relief at 0 hours and one hour after surgery. In contrast, the research conducted by Bennie concluded that preoperative acetaminophen failed to cause significant pain relief. Huang (18), Santos (16), and Zieliński (17) used the VAS scale to consistently demonstrate that preemptive acetaminophen effectively decreased pain scores at both one-2 hours and even 6-8 hours after surgery. Additionally, Fux-Noy (20), Raslan (21), and Zieliński (17) utilized the WB Faces scale to assess postoperative pain levels within 2.5 to 4 hours. Raslan and Zieliński's study revealed that the experimental group had significantly lower pain scores than the control group did. However, Fux-Noy's study did not provide sufficient evidence to substantiate the clinical effectiveness of acetaminophen as a preanalgesic agent. In Xuan's meta-analysis, which focused on the effect of preoperative acetaminophen in adult patients, the administration thereof was found to significantly reduce opioid consumption among patients within the initial 24 hours following general anesthesia, with lower pain scores at 12 hours after surgery (5). Arici's study has shown that in total abdominal hysterectomy, preemptive intravenous acetaminophen provided good-quality postoperative analgesia, with patients exhibiting decreased consumption of morphine and minimal side effects (23). Although adult patients' time points of postoperative pain relief differ from children's, Arici's results demonstrate that preemptive acetaminophen may effectively alleviate postoperative pain, which further supports our finding.

Rate of rescue analgesia, as an important metric, is frequently employed to reveal the intensity of postoperative pain. In Kano's study, the preoperative administration of intravenous acetaminophen before third molar surgery resulted in a notable reduction in the need for rescue analgesics and proved to be more efficacious in pain management than was postoperative administration or no treatment (24). In our review, 6 studies (46%) reported the use of postsurgical rescue analgesia. After analyzing 6 studies, we found that the

preemptive-analgesia group had a lower incidence of requiring rescue analgesia after surgery than the control group did, whichwas similar to the conclusion of Kano's study. Overall, preemptive acetaminophen may mitigate postoperative pain in children.

Postoperative nausea and vomiting are prevalent postoperative adverse events observed in pediatric patients. Previous research has demonstrated that acetaminophen wields a preventive effect on PONV. In the first place, acetaminophen blocks PONV by inhibiting certain serotonergic pathways in the central nervous system. In the second place, AM404, a metabolite of acetaminophen within the brain, indirectly augments the endocannabinoid system's activity to block PONV (10). Here, our study suggests that acetaminophen did not exert a preventive effect. Significantly, in Anderson's study, the high-dose acetaminophen group (100 mg/kg) failed to alleviate postoperative pain in children and even led to an increased incidence of PONV. Hence, more validation studies with larger sample sizes in multi-center settings are required to answer this question.

Previous studies indicated that oral administration was the most convenient and relatively cost-effective for clinical application (11). In the studies we analyzed, the predominant method of acetaminophen administration was indeed oral, with intravenous and rectal routes following suit. Various types of operations, namely strabismus surgery, laparoscopic hernia repair, myringotomy, adenotonsillectomy, and dental surgery are encompassed in this study. Interestingly, acetaminophen is used predominantly in pediatric otolaryngology and dental surgery, likely because children undergoing these procedures often experience severe postoperative pain, requiring additional pain relief treatments (17,21).

Preemptive analgesia, a commonly employed strategy for multimodal analgesia, has gained significant traction in the realm of adult medicine. However, to reiterate, its efficacy in pediatric patients remains a topic of debate. By analyzing several aspects of procedures that involved preoperative acetaminophen, such as the route of administration, type of operation, pain scores, and incidence of PONV, we made the first attempt to conduct a comprehensive meta-analysis and systematic review of the utilization of acetaminophen for preemptive analgesia in the pediatric population. Our findings indicate that preoperative acetaminophen can reduce postoperative pain in children and decrease the need for additional pain relief but not prevent postoperative nausea and vomiting. Therefore, we suggest that preemptive acetaminophen may be a beneficial strategy for enhancing perioperative pain management in pediatric patients.

The current study has some limitations. The randomized controlled trials (RCTs) incorporated in the analysis had restricted sample sizes, and the utilization of diverse pain scales and time points reduced the number of studies available for subgroup analysis. Because of this limited number of studies, publication bias and meta-regression were not assessed. Additionally, certain studies lacked adequate descriptions of patient randomization, blinding, and outcome assessment, thereby introducing a potential risk of bias. Furthermore, a notable degree of heterogeneity is evident. Currently, no widely accepted gold-standard scale for assessing pain scores exists, and the inconsistency in defining outcome measures leads to effect heterogeneity. Consequently, there is a pressing need for additional RCTs that are of high quality and well-managed.

Conclusions

In conclusion, this meta-analysis suggested that preemptive acetaminophen in children may decrease pain intensity and reduce dependence on pain rescue interventions but not prevent adverse effects such as nausea and vomiting, which potentially supports the inclusion of preemptive analgesia as a component of multimodal analgesic approaches for pediatric patients.

Author Contributions

WT, RZ, HX, and ZZ conceived the idea for the paper. XH performed screening, quality assessment, and data extraction. XH performed data analysis. XH drafted the first version of the article, and RZ critically revised the manuscript for important content. All authors discussed the results commented on the manuscript, and approved the final version to be published.

References

1. Loeser JD, Melzack R. Pain: An overview. *Lancet* 1999; 353:1607-1609.
2. Singh D, Kumar S, Lnu B, et al. Preemptive levetiracetam decreases postoperative pain: A double-blind, randomised, control trial. *Cureus* 2023; 15:e33281.
3. Madi D, Clinton M. Pain and its impact on the functional ability in children

treated at the Children's Cancer Center of Lebanon. *J Pediatr Nurs* 2018; 39:E11-E20.

4. Chatterjee US. Preemptive analgesia in paediatric surgery. *Afr J Paediatr Surg* 2011; 8:267-268.
5. Xuan C, Yan W, Wang D, et al. Efficacy of preemptive analgesia treatments for the management of postoperative pain: A network meta-analysis. *Br J Anaesth* 2022; 129:946-958.
6. Lin HQ, Jia DL. Effect of preemptive ketamine administration on postoperative visceral pain after gynecological laparoscopic surgery. *J Huazhong Univ Sci Technolog Med Sci* 2016; 36:584-587.
7. Mahmoud A, Abuelazm M, Ashraf Salah Ahmed A, et al. Early perioperative versus postoperative meloxicam for pain control in patients undergoing orthopedic surgery: a systematic review and Meta-analysis of randomized controlled trials. *Curr Med Res Opin* 2023; 39:113-122.
8. Ye Z, Zhu Y, Zhang R, et al. Effect of multimodal preemptive analgesia of flurbiprofen axetil, nalbuphine, and retrobulbar block on postoperative pain and enhanced recovery in patients undergoing oculoplastic day surgery: A prospective, randomized, double-blinded study. *Ophthalmic Plast Reconstr Surg* 2023; 39:260-265.
9. Parri N, Silvagni D, Chiarugi A, et al. Paracetamol and ibuprofen combination for the management of acute mild-to-moderate pain in children: Expert consensus using the Nominal Group Technique (NGT). *Ital J Pediatr* 2023; 49:36.
10. Jóźwiak-Bebenista M, Nowak JZ. Paracetamol: Mechanism of action, applications and safety concern. *Acta Pol Pharm* 2014; 71:11-23.
11. Cain KE, Iniesta MD, Fellman BM, et al. Effect of preoperative intravenous vs oral acetaminophen on postoperative opioid consumption in an enhanced recovery after surgery (ERAS) program in patients undergoing open gynecologic oncology surgery. *Gynecol Oncol* 2021; 160:464-468.
12. Andersen RD, Langius-Eklöf A, Nakstad B, Bernklev T, Jylli L. The measurement properties of pediatric observational pain scales: A systematic review of reviews. *Int J Nurs Stud* 2017; 73:93-101.
13. Bennie RE, Boehringer LA, McMahon S, Allen H, Dierdorf SF. Postoperative analgesia with preoperative oral ibuprofen or acetaminophen in children undergoing myringotomy. *Paediatr Anaesth* 1997; 7:399-403.
14. Mahgoobifard M, Mirmesdagh Y, Imani F, Najafi A, Nataj-Majd M. The analgesic efficacy of preoperative oral Ibuprofen and acetaminophen in children undergoing adenotonsillectomy: A randomized clinical trial. *Anesth Pain Med* 2014; 4:e15049-e15049.
15. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. *Scand J Pain* 2016; 13:67-75.
16. Santos PS, Massignan C, de Oliveira EV, et al. Does the pre-emptive administration of paracetamol or ibuprofen reduce trans- and post-operative pain in primary molar extraction? A randomized placebo-controlled clinical trial. *Int J Paediatr Dent* 2020; 30:782-790.
17. Zieliński J, Morawska-Kochman M, Dudek K, Czalpa M, Zatoński. The effect of pre-emptive analgesia on the postoperative pain in pediatric otolaryngology: A randomized, controlled trial. *J Clin Med* 2022; 11:2713.
18. Huang Junwei ZC, Wu Shuyun. Effect of different preemptive analgesia on multi-mode analgesia after laparoscopic surgery in children. *Int Med Health Guidance* 2014:20.
19. Felemban OM, Alshamrani RM, Aljeddawi DH, Bagher SM. Effect of virtual reality distraction on pain and anxiety during infiltration anesthesia in pediatric patients: A randomized clinical trial. *BMC Oral Health* 2021; 21:321.
20. Fux-Noy A, Bendahan Y, Ungar E, et al. Does preoperative paracetamol reduce pain after dental treatment? A randomized controlled double-blind study. *Quintessence Int* 2020; 51:732-740.
21. Raslan N, Zouzou T. Comparison of preemptive ibuprofen, acetaminophen, and placebo administration in reducing peri- and postoperative pain in primary tooth extraction: A randomized clinical trial. *Clin Exp Dent Res* 2021; 7:1045-1052.
22. Takeda Y, Fukunishi S, Nishio S, Yoshiya S, Hashimoto K, Simura Y. Evaluating the effect of intravenous acetaminophen in multimodal analgesia after total hip arthroplasty: A randomized controlled trial. *J Arthroplasty* 2019; 34:1155-1161.
23. Arici S, Gurbet A, Türker G, Yavaşcaoğlu B, Sahrin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri* 2009; 21:54-61.
24. Kano K, Kawamura K, Miyake T. Effects of preemptive analgesia with intravenous acetaminophen on postoperative pain relief in patients undergoing third molar surgery: A prospective, single-blind, randomized controlled trial. *Med Oral Patol Oral Cir Bucal* 2021; 26:e64-e70.
25. Derkay CS, Wadsworth JT, Darrow DH, Strasnick B, Thompson GK, O'Master J. Tube placement: A prospective, randomized double-blind study. *Laryngoscope* 1998; 108:97-101.
26. Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *Eur J Clin Pharmacol* 2001;57:559-569.
27. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. *Int J Paediatr Dent* 2011; 21:306-313.
28. Aksoy M, Ince I, Ahiskalioglu A, Keles S, Doymus O. Effect of intravenous preoperative versus postoperative paracetamol on postoperative nausea and vomiting in patients undergoing strabismus surgery: A prospective randomized study. *Agri* 2018; 30:1-7.
29. Abou El Fadl R, Gowely M, Helmi M, Obeid M. Effects of pre-emptive analgesia on efficacy of buccal infiltration during pulpotomy of mandibular primary molars: a double-blinded randomized controlled trial. *Acta Odontol Scand* 2019; 77:552-558.
30. Kharouba J, Ratson T, Somri M, Blumer S. Preemptive analgesia by paracetamol, ibuprofen or placebo in pediatric dental care: A randomized controlled study. *J Clin Pediatr Dent* 2019; 43:51-55.