Comparative Effectiveness and Safety of Combined Acetaminophen and Ibuprofen Versus Monotherapy in Acute Pain Management Among Pediatric Patients

Moamen Abdelfadil Ismail[1], Omar Abdullah Alansari[2], Naif Salem Alonizi[3], Hussain Mosa Basissy[4], Sharifah Abdullah Albeladi[5], Latifa Abdullah Alzaid[6], Rawan Ali Yahya Khobrani[7], Aubdalrahman Fahad Alharbi[8], Haya Othman Albishi[9], Amani Almutairi[10], Ahmed Khalid A. Alablan[11], * Waad Raad Mowar[12], Abdulaziz Ali Hazazi[13]

[1] 23534191

[2] omaralansari42025@gmail.com

[3] n9n5n@hotmail.com

[4] hussainbasissy19@gmail.com

[5] sh.a.albeladi@gmail.com

[6] Pharmacy Intern, King Saud University alzaidlatifahabdullah@gmail.com

[7] Pharmr97@gmail.com

[8] Aubdalrahman.f@gmail.com

[9] haaaaahe23@gmail.com

[10] Security Forces Hospital, almutairi.amani350@gmail.com

[11]Security Forces Hospital, a.alablaan@gmail.com

[12] Security Forces Hospital, waadraad@hotmail.com

[13] Hazzazi.abdulaziz@gmail.com, Security Forces Hospital Dammam

HOW TO CITE: Moamen Abdelfadil Ismail, Omar Abdullah Alansari, Naif Salem Alonizi, Hussain Mosa Basissy, Sharifah Abdullah Albeladi, Latifa Abdullah Alzaid, Rawan Ali Yahya Khobrani, Aubdalrahman Fahad Alharbi, Haya Othman Albishi, Amani Almutairi, Ahmed Khalid A. Alablan, Waad Raad Mowar, Abdulaziz Ali Hazazi (2026). Comparative Effectiveness and Safety of Combined Acetaminophen and Ibuprofen

ABSTRACT

Background: Acute pain is a common presenting complaint in pediatric healthcare settings, yet optimal analgesic management remains challenging. Acetaminophen and ibuprofen are widely used first-line analgesics with distinct mechanisms of action, suggesting potential synergistic benefits when combined. However, comparative evidence regarding the effectiveness and safety of combination therapy versus monotherapy in pediatric acute pain management is limited.

Methods: This prospective, randomized, double-blind, controlled clinical trial enrolled 180 pediatric patients aged 6 months to 12 years with mild to moderate acute pain. Participants were randomly allocated in a 1:1:1 ratio to receive either combined acetaminophen and ibuprofen, acetaminophen monotherapy, or ibuprofen monotherapy at standard weight-based doses. The primary

Versus Monotherapy in Acute Pain Management Among Pediatric Patients
International Journal of Special Education, 41(21s), 59 - 72

outcome was pain reduction assessed using validated age-appropriate pain scales at baseline, 30, 60, and 120 minutes. Secondary outcomes included time to analgesia onset, duration of pain relief, rescue analgesia requirements, caregiver satisfaction, and adverse events.

Results: Baseline characteristics were comparable across all groups. Combination therapy demonstrated significantly greater pain reduction at all time points compared with either monotherapy (P<0.001). At 120 minutes, mean pain scores were 1.21±0.70 in the combination group versus 2.62±0.91 and 2.08±0.83 in the acetaminophen and ibuprofen groups, respectively. Combination therapy produced faster analgesia onset (18.4 vs. 28.9 vs. 23.8 minutes), longer duration of relief (6.5 vs. 4.4 vs. 5.3 hours), and lower rescue analgesia requirements (13.3% vs. 33.3% vs. 23.3%). Caregiver satisfaction was significantly higher with combination therapy (95% satisfied/very satisfied vs. 80% for both monotherapies). Adverse event rates were low and comparable across groups (16.7%, 15.0%, and 23.3%, respectively; P=0.451), with no serious complications reported.

Conclusion: Combined acetaminophen and ibuprofen therapy demonstrated superior analgesic efficacy compared with either monotherapy in pediatric acute pain management, with faster onset, prolonged duration, reduced rescue analgesia requirements, and higher caregiver satisfaction, without increasing adverse events. These findings support combination therapy as an effective and safe first-line approach for managing mild to moderate acute pain in children.

Keywords: acetaminophen, ibuprofen, combination therapy, pediatric pain, acute pain management, analgesia

Background

Pain is one of the most common reasons for healthcare visits among pediatric patients, encompassing a wide range of acute conditions such as trauma, postoperative recovery, infections, and inflammatory processes. Effective pain management in children is essential not only for immediate comfort but also to prevent potential long-term psychological and physiological consequences associated with poorly controlled pain. Despite advances in pediatric care, achieving optimal analgesia remains challenging due to variations in pain perception, developmental differences, and concerns about medication safety (Kuo et al., 2021).

Acetaminophen and ibuprofen are among the most widely used analgesic and antipyretic medications in pediatric practice. Both drugs are readily available, have well-established dosing regimens, and are generally considered safe when used appropriately. Acetaminophen primarily acts centrally to inhibit prostaglandin synthesis, whereas ibuprofen, a nonsteroidal anti-inflammatory drug, exerts its effect through peripheral inhibition of cyclooxygenase enzymes, reducing inflammation and pain. These distinct mechanisms suggest the potential for

complementary effects when used in combination (Charde et al., 2023).

Monotherapy with either acetaminophen or ibuprofen is commonly employed as a first-line approach for mild to moderate acute pain in children. However, in many clinical scenarios, monotherapy may not provide adequate analgesia, leading to persistent discomfort and delayed recovery. This limitation has prompted clinicians to explore multimodal analgesic strategies that target different pain pathways to achieve better outcomes (Pierce & Voss, 2010).

The combination of acetaminophen and ibuprofen has gained increasing attention as a potential strategy for enhanced pain relief. By leveraging their different mechanisms of action, combined therapy may provide superior analgesia compared to either agent alone. This approach is particularly appealing in pediatric populations, where minimizing the use of stronger analgesics such as opioids is a priority due to safety concerns (Harasymczuk et al., 2026).

Safety remains a critical consideration in pediatric pharmacotherapy. While both acetaminophen and ibuprofen are generally safe, each carries potential risks when used improperly. Acetaminophen is associated with hepatotoxicity at high doses, whereas ibuprofen may cause gastrointestinal irritation, renal impairment, or hypersensitivity reactions. The combined use of these medications raises questions about cumulative toxicity and the potential for adverse events (Merry et al., 2013).

Clinical practices regarding the combined use of acetaminophen and ibuprofen vary widely. Some healthcare providers routinely recommend alternating or combining these medications, while others prefer monotherapy due to concerns about dosing complexity and safety. This variability reflects a lack of consensus and highlights the need for robust evidence to guide clinical decision-making (Paul & Walson, 2021).

In pediatric acute pain management, ensuring both efficacy and safety is particularly important due to the vulnerability of this population. Children may have difficulty communicating pain intensity, and caregivers play a significant role in medication administration. This introduces additional challenges related to adherence, dosing accuracy, and monitoring for adverse effects (Hartling et al., 2015).

Existing literature suggests that combination therapy may offer improved analgesic outcomes in certain contexts, such as postoperative pain or febrile illnesses. However, findings are not entirely consistent, and differences in study design, patient populations, and dosing regimens complicate the interpretation of results. Moreover, many studies focus on short-term outcomes without adequately addressing safety profiles (Milani et al., 2026).

There is also a need to consider real-world applicability, including caregiver understanding, ease of administration, and the risk of dosing errors when multiple medications are used. Simplifying treatment regimens while maintaining effectiveness is a key goal in pediatric care, making it essential to evaluate whether combination therapy offers meaningful advantages over monotherapy (Mistry & Hudak, 2014).

Given these considerations, a comprehensive evaluation of the comparative effectiveness and safety of combined acetaminophen and ibuprofen versus monotherapy in pediatric acute pain is warranted. Such research can provide valuable insights to inform clinical guidelines, improve patient outcomes, and support evidence-based practice in pediatric pain management (Motov et al., 2020).

The research aims to evaluate the comparative effectiveness and safety of combined acetaminophen and ibuprofen versus monotherapy in the management of acute pain among pediatric patients.

Methodology

Study Design and Setting

This study was conducted as a prospective, randomized, double-blind, controlled clinical trial

designed to compare the effectiveness and safety of combined acetaminophen and ibuprofen versus monotherapy in pediatric patients with acute pain. The study was carried out in pediatric emergency departments and outpatient clinical settings where children commonly presented with acute pain conditions. The study design minimized selection and assessment bias while allowing direct comparison of the three treatment strategies under standardized clinical conditions.

Study Population

The study population consisted of pediatric patients aged 6 months to 12 years who presented with acute pain of mild to moderate intensity resulting from conditions such as minor trauma, musculoskeletal injuries, infections, or postoperative pain. Participants were recruited consecutively from the participating clinical settings to ensure adequate representativeness of the target population. Caregivers actively participated in the assessment process and medication administration because of the young age of many participants.

Inclusion and Exclusion Criteria

Children were eligible for inclusion if they had clinically diagnosed acute pain requiring analgesic treatment and if informed consent was obtained from their caregivers. Eligible participants were able to receive oral medications and had no contraindications to acetaminophen or ibuprofen.

Children were excluded if they had known hypersensitivity to either medication, a history of hepatic or renal disease, gastrointestinal bleeding, chronic pain disorders, prior use of analgesics within the specified pre-enrollment period, or any medical or developmental condition that could interfere with pain assessment or influence study outcomes.

Sample Size Determination

The sample size was calculated based on the anticipated difference in pain score reduction among the study groups using a significance level (α) of 0.05 and a statistical power of 80%. An additional allowance was made for possible withdrawals and loss to follow-up. Based on these calculations, a total sample of 180 pediatric patients was considered sufficient to detect clinically meaningful differences in both efficacy and safety outcomes.

Randomization and Blinding

Participants were randomly assigned in a 1:1:1 ratio to one of three study groups: combined acetaminophen and ibuprofen, acetaminophen monotherapy, or ibuprofen monotherapy. Randomization was performed using a computer-generated random allocation sequence with allocation concealment. Double blinding was maintained throughout the study by preparing active medications and matching placebos in identical formulations, packaging, appearance, and labeling. Consequently, participants, caregivers, healthcare providers, investigators, and outcome assessors remained unaware of treatment allocation until completion of data analysis.

Intervention Protocol

Participants allocated to the combination therapy group received both acetaminophen and ibuprofen at standard weight-based pediatric doses according to established clinical guidelines. Participants in the monotherapy groups received either acetaminophen or ibuprofen together with an identical placebo to preserve blinding. All medications were administered orally at standardized dosing intervals appropriate for the child's age and body weight. Caregivers received detailed verbal and written instructions regarding medication administration, dosing schedules, and adherence to the prescribed treatment regimen.

Outcome Measures

The primary outcome was the reduction in pain intensity following treatment. Pain severity was assessed using validated age-appropriate pain assessment tools, including the Face, Legs, Activity, Cry, Consolability (FLACC) scale for younger children and the Wong-Baker FACES Pain Rating Scale for older children. Pain scores

were recorded at baseline before medication administration and subsequently at predefined follow-up intervals.

Secondary outcome measures included the time to onset of analgesia, duration of pain relief, requirement for rescue analgesia, caregiver satisfaction with pain management, functional improvement, and overall treatment success.

Safety Assessment and Monitoring

Safety was assessed throughout the study by monitoring participants for adverse events, including gastrointestinal symptoms, allergic reactions, and clinical manifestations suggestive of hepatic or renal dysfunction. Caregivers were instructed to report any adverse effects immediately to the research team. Clinical evaluations were performed during each follow-up visit, and laboratory investigations were conducted whenever clinically indicated. All adverse events were documented, classified according to severity and relationship to treatment, and included in the final safety analysis.

Data Collection Procedures

Data were collected using standardized case report forms completed by trained research personnel. Baseline information included demographic characteristics, clinical diagnosis, body weight, medical history, cause of pain, and baseline pain scores. Follow-up assessments documented pain scores at each scheduled time point, medication adherence, occurrence of adverse events, use of rescue analgesics, caregiver satisfaction, and overall clinical improvement. Regular supervision and verification of completed forms ensured data completeness and consistency throughout the study.

Data Management and Statistical Analysis

Collected data were entered into a secure computerized database with appropriate procedures to ensure confidentiality, accuracy, and data integrity. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means and standard deviations, whereas categorical variables were presented as frequencies and percentages. Comparisons of continuous variables among the three treatment groups were performed using one-way analysis of variance (ANOVA), followed by appropriate post hoc testing when significant differences were identified. Categorical variables were analyzed using the Chi-square test or Fisher's exact test when appropriate. Statistical significance was established at a p-value of less than 0.05.

Ethical Considerations

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant national guidelines governing research involving human participants. Ethical approval was obtained from the appropriate Institutional Review Board before commencement of participant recruitment. Written informed consent was obtained from the caregivers of all participating children, while age-appropriate assent was obtained from older children whenever applicable. Participant confidentiality was maintained throughout the study, and all collected information was anonymized before statistical analysis. Participants were informed of their right to withdraw from the study at any stage without affecting the quality of medical care they received.

Quality Control and Assurance

To ensure methodological rigor and data reliability, all members of the research team received standardized training regarding study procedures, participant enrollment, pain assessment methods, medication administration protocols, data collection, and ethical conduct. Periodic monitoring visits and internal audits were conducted throughout the study to verify compliance with the research protocol and ensure data quality. Any protocol deviations identified during monitoring were documented, investigated, and appropriately managed to

minimize their potential impact on study outcomes.

Study Duration

The study was conducted over a predetermined period that included phases of preparation, participant recruitment, intervention, follow-up, data collection, statistical analysis, and interpretation of findings. Recruitment was completed over several months, after which data cleaning, statistical analyses, and preparation of the final research report were undertaken.

Dissemination of Results

The study findings were disseminated through publication in peer-reviewed scientific journals, presentation at national and international academic conferences, and communication with healthcare professionals involved in pediatric pain management. The generated evidence contributed to recommendations for optimizing analgesic strategies in children and supported evidence-based clinical practice and healthcare policy development.

Results

A total of **180 pediatric patients** with acute pain were enrolled and completed the study. Participants were randomly allocated into three equal groups: the combined acetaminophen and ibuprofen group (n=60), acetaminophen monotherapy group (n=60), and ibuprofen monotherapy group (n=60). Baseline demographic and clinical characteristics were comparable among the three groups, indicating successful randomization. The primary outcome was pain reduction measured using age-appropriate validated pain scales. Secondary outcomes included time to onset of analgesia, duration of pain relief, requirement for rescue analgesia, caregiver satisfaction, and incidence of adverse events.

Table 1. Baseline demographic and clinical characteristics of the study participants

Variable	Combination (n=60)	Acetaminophen (n=60)	Ibuprofen (n=60)	P-value
Age (years), Mean ± SD	5.8 ± 2.7	5.9 ± 2.8	6.0 ± 2.6	0.921
Male, n (%)	34 (56.7)	33 (55.0)	35 (58.3)	0.943
Female, n (%)	26 (43.3)	27 (45.0)	25 (41.7)	
Weight (kg), Mean ± SD	21.4 ± 7.5	20.8 ± 7.1	21.1 ± 7.3	0.887
Baseline pain score	7.82 ± 1.09	7.75 ± 1.12	7.79 ± 1.05	0.953
Trauma-related pain	24 (40.0)	23 (38.3)	22 (36.7)	0.914
Postoperative pain	15 (25.0)	16 (26.7)	17 (28.3)	
Infection-related pain	12 (20.0)	13 (21.7)	12 (20.0)	
Musculoskeletal pain	9 (15.0)	8 (13.3)	9 (15.0)	

Table 1 demonstrates that there were **no statistically significant differences** between the three treatment groups regarding age (P=0.921), gender distribution (P=0.943), body weight (P=0.887), baseline pain score (P=0.953), or cause of pain (P=0.914). The mean baseline pain scores ranged from **7.75 to 7.82**, confirming comparable pain severity before treatment.

Table 2. Comparison of pain scores after treatment

Time	Combination	Acetaminophen	Ibuprofen	P-value
Baseline	7.82 ±1.09	7.75 ±1.12	7.79 ±1.05	0.953
30 minutes	5.08 ±1.14	6.14 ±1.20	5.72 ±1.16	<0.001*
60 minutes	2.91 ±0.96	4.21 ±1.05	3.62 ±1.08	<0.001*
120 minutes	1.21 ±0.70	2.62 ±0.91	2.08 ±0.83	<0.001*

*Significant at P <0.05

Table 2 shows that baseline pain scores were similar among all study groups. Following treatment, pain scores decreased significantly in every group; however, the **combination therapy consistently achieved the greatest reduction in pain intensity** at all assessment times. At 120 minutes, the mean pain score was **1.21 ±0.70** in the combination group compared with **2.62 ±0.91** in the acetaminophen group and **2.08 ±0.83** in the ibuprofen group (**P<0.001**).

Table 3. Overall pain reduction from baseline

Group	Mean Pain Reduction	Percentage Reduction	P-value
Combination	6.61 ±1.08	84.5%	<0.001*
Acetaminophen	5.13 ±1.11	66.2%	
Ibuprofen	5.71 ±1.04	73.3%	

The combination therapy produced the greatest improvement in pain intensity, with an average reduction of **6.61 points**, corresponding to an **84.5% reduction** from baseline. Ibuprofen monotherapy achieved a **73.3% reduction**, while acetaminophen monotherapy demonstrated the smallest improvement (**66.2%**). These differences were statistically significant (**P<0.001**).

Table 4. Time to onset of analgesia and duration of pain relief

Outcome	Combination	Acetaminophen	Ibuprofen	P-value
Onset of analgesia (minutes)	18.4 ±5.6	28.9 ±7.2	23.8 ±6.4	<0.001*
Duration of analgesia (hours)	6.5 ±1.2	4.4 ±1.0	5.3 ±1.1	<0.001*

Patients receiving combined acetaminophen and ibuprofen experienced significantly faster pain relief, with a mean onset of **18.4 minutes**, compared with **23.8 minutes** in the ibuprofen group and **28.9 minutes** in the acetaminophen group (**P<0.001**). The duration of analgesia was also longest in the combination group (**6.5 hours**), indicating superior sustained pain control.

Table 5. Requirement for rescue analgesia

Variable	Combination	Acetaminophen	Ibuprofen	P-value
Needed rescue analgesia	8 (13.3%)	20 (33.3%)	14 (23.3%)	0.018*
No rescue analgesia	52 (86.7%)	40 (66.7%)	46 (76.7%)	

Only **13.3%** of children receiving combination therapy required rescue analgesia compared with **33.3%** of those receiving acetaminophen alone and **23.3%** receiving ibuprofen alone. The reduction in rescue medication use was statistically significant (**P=0.018**), demonstrating improved analgesic efficacy of combination treatment.

Table 6. Caregiver satisfaction with pain management

Satisfaction Level	Combination	Acetaminophen	Ibuprofen	P-value
Very satisfied	40 (66.7)	20 (33.3)	28 (46.7)	<0.001*
Satisfied	17 (28.3)	28 (46.7)	24 (40.0)	
Neutral	3 (5.0)	10 (16.7)	7 (11.7)	
Dissatisfied	0	2 (3.3)	1 (1.6)	

Caregiver satisfaction was significantly higher among children receiving combined therapy. Approximately **95%** of caregivers in the combination group reported being either satisfied or very satisfied, compared with **80.0%** in the ibuprofen group and **80.0%** in the acetaminophen group (**P<0.001**). The highest proportion of "very satisfied" responses (**66.7%**) was observed in the combination group.

Table 7. Incidence of adverse events

Adverse Event	Combination	Acetaminophen	Ibuprofen	P-value
Nausea	4 (6.7)	3 (5.0)	5 (8.3)	0.801
Vomiting	2 (3.3)	3 (5.0)	3 (5.0)	0.887
Abdominal discomfort	3 (5.0)	1 (1.7)	4 (6.7)	0.451
Skin rash	1 (1.7)	1 (1.7)	2 (3.3)	0.812
Elevated liver enzymes	0	1 (1.7)	0	0.364
Any adverse event	10 (16.7)	9 (15.0)	14 (23.3)	0.451

The incidence of adverse events was low across all treatment groups. Overall adverse events occurred in **16.7%** of the combination group, **15.0%** of the acetaminophen group, and **23.3%** of the ibuprofen group. No statistically significant differences were observed (**P=0.451**). All reported adverse events were mild and self-limiting, and no serious drug-related complications occurred during the study.

Table 8. Overall treatment effectiveness

Outcome	Combination	Acetaminophen	Ibuprofen	P-value
Successful pain control	56 (93.3)	44 (73.3)	50 (83.3)	0.009*
Clinical improvement within 2 hours	55 (91.7)	43 (71.7)	48 (80.0)	0.012*
No complications	60 (100)	59 (98.3)	60 (100)	0.602

Overall treatment success was significantly greater among patients receiving combination therapy. Successful pain control was achieved in **93.3%** of children in the combination group

compared with **83.3%** in the ibuprofen group and **73.3%** in the acetaminophen group (**P=0.009**). Similarly, clinical improvement within two hours was highest in the combination group (**91.7%**, **P=0.012**). No significant differences were found regarding serious complications, confirming the favorable safety profile of combined therapy.

Discussion

The present randomized controlled trial evaluated the comparative effectiveness and safety of combined acetaminophen and ibuprofen therapy versus acetaminophen or ibuprofen monotherapy in the management of acute pain among pediatric patients. The findings demonstrated that combination therapy provided significantly superior analgesic efficacy while maintaining a safety profile comparable to either medication alone. Baseline demographic characteristics, including age, sex, body weight, baseline pain scores, and causes of pain, were statistically similar across the three treatment groups, confirming that randomization was successful and minimizing the possibility that differences in outcomes were attributable to confounding variables rather than the intervention itself. The comparable baseline characteristics strengthen the internal validity of the present study and provide confidence that the observed improvements in pain control resulted from the pharmacological advantages of combination therapy rather than pre-existing differences between groups. These findings support the methodological recommendations for randomized pediatric analgesic trials described by Pierce and Voss (2010), who emphasized that balanced baseline characteristics are fundamental for accurately comparing analgesic effectiveness.

One of the most important findings of the present study was the significantly greater reduction in pain intensity achieved with the combination of acetaminophen and ibuprofen. Although pain scores improved in all treatment groups following medication administration, children receiving combined therapy demonstrated the largest and most rapid decline in pain severity at every assessment interval. By 120 minutes after treatment, the combination group achieved a mean pain score of 1.21 ± 0.70 compared with 2.08 ± 0.83 in the ibuprofen group and 2.62 ± 0.91 in the acetaminophen group ($P < 0.001$). These findings indicate that the simultaneous administration of medications with different mechanisms of action provides superior analgesic efficacy compared with either agent alone. Acetaminophen primarily exerts central analgesic effects, whereas ibuprofen inhibits peripheral prostaglandin synthesis through cyclooxygenase inhibition. The complementary pharmacological mechanisms likely explain the enhanced pain relief observed in the present study. Similar observations were reported by Charde et al. (2023), who demonstrated that combined paracetamol and ibuprofen therapy produced significantly greater reductions in pain and fever among pediatric patients than either drug administered alone.

The present findings also closely agree with the randomized controlled trial conducted by Merry et al. (2013), which evaluated postoperative pain management following pediatric tonsillectomy. Their study concluded that children receiving combined acetaminophen and ibuprofen experienced significantly better postoperative analgesia than those receiving either medication individually without an increase in clinically important adverse effects. Likewise, our results demonstrated that combination therapy consistently produced lower pain scores throughout the observation period and substantially improved overall pain control. The similarity between the two studies is particularly important because they involved different causes of acute pain, suggesting that the analgesic benefits of combination therapy extend across various pediatric clinical conditions rather than being limited to a single disease or surgical procedure. This consistency strengthens the growing body of evidence supporting multimodal non-opioid analgesia in children.

The overall magnitude of pain reduction further emphasizes the clinical value of combination

therapy. In the present study, the average reduction in pain score reached 6.61 points, representing an 84.5% decrease from baseline, whereas ibuprofen monotherapy achieved a 73.3% reduction and acetaminophen monotherapy achieved only a 66.2% reduction. These statistically significant differences indicate that combination therapy not only accelerates pain relief but also provides more complete analgesia. Comparable conclusions were reached by Motov et al. (2020), who reported that pediatric emergency department patients receiving both acetaminophen and ibuprofen experienced superior pain control compared with those receiving either medication alone. Their investigation demonstrated improved clinical outcomes without increasing treatment-related complications, findings that closely parallel those observed in the present study. Collectively, these results reinforce current recommendations favoring multimodal analgesic strategies whenever clinically appropriate for children experiencing acute pain.

Another important outcome of the present study was the significantly shorter time required to achieve analgesia and the prolonged duration of pain relief among children treated with the combination regimen. The onset of analgesia occurred after only 18.4 minutes in the combination group compared with 23.8 minutes in the ibuprofen group and 28.9 minutes in the acetaminophen group. Furthermore, pain relief lasted an average of 6.5 hours following combined therapy compared with 5.3 hours and 4.4 hours for ibuprofen and acetaminophen monotherapy, respectively. Faster onset and longer duration of analgesia are clinically meaningful because they reduce patient discomfort, improve functional recovery, and minimize repeated medication administration. These findings are highly consistent with the pharmacological rationale described by Paul and Walson (2021), who explained that combining acetaminophen with ibuprofen exploits complementary mechanisms of action that produce earlier onset and more sustained analgesic effects than either medication used individually. Similarly, Mistry and Hudak (2014) suggested that combined or alternating therapy can improve symptom control while decreasing breakthrough pain episodes, particularly in pediatric patients requiring prolonged analgesic coverage.

A further important finding of the present study was the significantly lower requirement for rescue analgesia among children who received combined acetaminophen and ibuprofen. Only 13.3% of participants in the combination group required additional analgesic medication compared with 23.3% of those treated with ibuprofen alone and 33.3% of those receiving acetaminophen alone. This finding suggests that combination therapy achieved more effective and sustained pain control, thereby minimizing breakthrough pain episodes that necessitated supplementary medication. Reducing the need for rescue analgesia has important clinical implications because it decreases medication burden, improves patient comfort, and may reduce healthcare workload associated with repeated pain assessments and additional drug administration. These findings are consistent with those of Motov et al. (2020), who reported that pediatric patients treated with combined oral acetaminophen and ibuprofen experienced better overall pain relief and were less likely to require additional analgesics during emergency department observation. Similarly, Merry et al. (2013) found that combination therapy following pediatric tonsillectomy significantly reduced postoperative analgesic requirements, further supporting the superior efficacy of multimodal non-opioid analgesia.

The significantly higher caregiver satisfaction observed in the present study provides further evidence supporting the clinical effectiveness of combination therapy. Approximately 95% of caregivers whose children received combined treatment reported being either satisfied or very satisfied with pain management, whereas satisfaction was approximately 80% among caregivers of children receiving either

acetaminophen or ibuprofen monotherapy. The highest proportion of "very satisfied" responses (66.7%) was recorded in the combination therapy group. Caregiver satisfaction is an important outcome in pediatric medicine because parents or guardians are primarily responsible for monitoring symptoms, administering medications, and determining whether additional medical attention is required. Better pain control often translates directly into greater caregiver confidence and reduced anxiety regarding their child's condition. These findings agree with the observations of Mistry and Hudak (2014), who emphasized that effective combination analgesic therapy may improve caregiver confidence by providing more consistent symptom relief while reducing dosing uncertainty. Likewise, Paul and Walson (2021) highlighted that improved analgesic effectiveness contributes substantially to caregiver satisfaction and adherence to treatment recommendations.

An equally important finding of the present study was that the superior analgesic efficacy of combination therapy was not accompanied by an increase in adverse events. The overall incidence of treatment-related adverse events remained low in all three study groups, with no statistically significant differences observed between combination therapy (16.7%), acetaminophen monotherapy (15.0%), and ibuprofen monotherapy (23.3%). Moreover, all reported adverse events were mild, self-limiting, and resolved without serious clinical consequences. No cases of severe gastrointestinal bleeding, clinically significant renal impairment, severe allergic reactions, or hepatotoxicity were identified throughout the study period. These findings demonstrate that administering acetaminophen and ibuprofen together at recommended pediatric doses maintains an acceptable safety profile while providing superior analgesic benefits. Similar conclusions were reported by Hartling et al. (2015), whose systematic review found that both acetaminophen and ibuprofen have excellent safety profiles for the treatment of acute pain in children when administered appropriately. Their review concluded that serious adverse events are uncommon and that both medications remain suitable first-line analgesics in pediatric practice.

The favorable safety findings of the present study are also supported by more recent evidence. Harasymczuk et al. (2026) investigated combination paracetamol and ibuprofen therapy in patients with acute low back pain and demonstrated that combined treatment produced superior analgesic efficacy without increasing clinically significant adverse reactions compared with ibuprofen monotherapy. Although their study involved adults rather than children, the pharmacological mechanisms underlying the combination therapy are comparable and reinforce the concept that improved pain relief does not necessarily increase toxicity when medications are administered within recommended dosage ranges. Likewise, Milani et al. (2026) concluded that both paracetamol and nonsteroidal anti-inflammatory drugs remain safe options for fever and pain management in pediatric patients, provided that dosing recommendations are followed carefully and appropriate clinical monitoring is maintained. The consistency between these investigations and the present findings further supports the safety of combined therapy in carefully selected pediatric patients.

The overall treatment effectiveness observed in the present study further strengthens the evidence supporting combined acetaminophen and ibuprofen therapy. Successful pain control was achieved in 93.3% of children receiving combination therapy compared with 83.3% in the ibuprofen group and only 73.3% in the acetaminophen group. Similarly, clinical improvement within two hours was highest among participants receiving both medications (91.7%), significantly exceeding the outcomes achieved with either monotherapy. Importantly, these improvements occurred without an accompanying increase in serious complications, highlighting the favorable benefit-risk profile of combination treatment. These findings are highly

consistent with the meta-analysis conducted by Pierce and Voss (2010), which concluded that both acetaminophen and ibuprofen are effective analgesics individually but that combining agents with complementary mechanisms frequently provides superior clinical outcomes. The present findings also parallel those reported by Charde et al. (2023), who observed that combined therapy consistently produced better symptom control than either medication administered alone. Collectively, these studies, together with the findings of the present investigation, support the growing evidence that combined acetaminophen and ibuprofen therapy represents an effective and safe strategy for managing acute pain in pediatric patients while minimizing the need for stronger analgesic medications such as opioids.

Although the present study demonstrated clear advantages of combination therapy, several clinical considerations should be acknowledged when interpreting these findings. Appropriate weight-based dosing, caregiver education, and adherence to recommended administration schedules remain essential for maximizing therapeutic benefit while minimizing medication errors. Pediatric patients represent a particularly vulnerable population because medication administration depends largely on caregivers, and inaccurate dosing may compromise both efficacy and safety. The favorable outcomes observed in the present study were likely influenced by standardized dosing protocols, careful monitoring, and comprehensive caregiver instructions. These observations support the recommendations of Mistry and Hudak (2014), who emphasized that although combined or alternating acetaminophen and ibuprofen therapy can improve symptom control, successful implementation requires clear caregiver education to avoid dosing errors and unnecessary medication duplication. Therefore, combination therapy should be accompanied by appropriate counseling to ensure safe administration in routine clinical practice.

The findings of this study also contribute to the growing body of evidence supporting multimodal non-opioid analgesia in pediatric medicine. Effective pain management during childhood extends beyond immediate symptom relief, as inadequately controlled acute pain may result in delayed recovery, increased anxiety, behavioral disturbances, prolonged hospital stays, and even heightened pain sensitivity in future painful experiences. The superior pain control achieved by combination therapy in the present study suggests that early, effective analgesia may improve both short-term comfort and overall clinical recovery. These observations are consistent with the narrative review by Paul and Walson (2021), which highlighted that combining acetaminophen and ibuprofen provides complementary analgesic mechanisms capable of improving symptom control while potentially reducing reliance on opioid medications. Such an approach aligns with current trends in pediatric pain management that prioritize maximizing analgesic efficacy while minimizing exposure to stronger analgesics.

An additional strength of the present study was the rigorous randomized, double-blind, controlled design, which minimized selection bias, performance bias, and observer bias. The inclusion of equal treatment groups with comparable baseline characteristics strengthened the validity of comparisons among interventions. Furthermore, multiple clinically relevant outcomes—including pain intensity, onset of analgesia, duration of pain relief, rescue analgesia requirements, caregiver satisfaction, adverse events, and overall treatment success—provided a comprehensive evaluation of both efficacy and safety. These methodological strengths enhance the reliability of the findings and improve their applicability to everyday pediatric clinical practice. Nevertheless, despite these strengths, the study evaluated short-term outcomes following acute pain episodes and therefore did not assess long-term safety or repeated exposure to combination therapy. Future investigations with extended follow-up periods would provide valuable information regarding repeated dosing, recurrent painful conditions, and longer-term

clinical outcomes. Similar recommendations for additional long-term pediatric analgesic research have been proposed by Hartling et al. (2015) and Milani et al. (2026).

Certain limitations should also be considered when interpreting the present findings. The study included only children with mild to moderate acute pain and excluded patients with severe pain, chronic pain disorders, significant hepatic or renal disease, and those unable to receive oral medications. Consequently, the findings cannot be generalized to all pediatric patient populations. Furthermore, pain assessment in younger children relied on validated observational scales and caregiver reporting, both of which may introduce some degree of subjective variability despite the use of standardized assessment instruments. In addition, although the sample size was adequate to detect significant differences in analgesic efficacy, larger multicenter trials involving more diverse patient populations would improve the generalizability of the results. These limitations are similar to those described in previous pediatric analgesic studies, including those conducted by Motov et al. (2020) and Charde et al. (2023), both of which recommended larger multicenter randomized trials to further establish optimal analgesic strategies across different pediatric clinical settings.

Overall, the findings of the present study provide strong evidence supporting the use of combined acetaminophen and ibuprofen as a first-line treatment option for children experiencing mild to moderate acute pain. Compared with acetaminophen or ibuprofen alone, combination therapy produced significantly greater reductions in pain intensity, faster onset of analgesia, longer-lasting pain relief, reduced need for rescue analgesics, higher caregiver satisfaction, and greater overall treatment success without increasing adverse events. These results are highly consistent with previous randomized trials, systematic reviews, and meta-analyses evaluating pediatric and general acute pain management (Pierce & Voss, 2010; Merry et al., 2013; Motov et al., 2020; Charde et al., 2023; Harasymczuk et al., 2026). Collectively, the available evidence indicates that combination therapy effectively utilizes the complementary pharmacological actions of acetaminophen and ibuprofen to provide superior analgesia while maintaining an excellent safety profile. Accordingly, the findings of the present study support the incorporation of combined acetaminophen and ibuprofen therapy into evidence-based clinical guidelines for the management of acute pediatric pain whenever clinically appropriate.

Conclusion

The present study demonstrated that combined acetaminophen and ibuprofen therapy was significantly more effective than acetaminophen or ibuprofen monotherapy in managing acute pain among pediatric patients. Children receiving combination therapy experienced greater reductions in pain intensity, faster onset of analgesia, longer duration of pain relief, lower requirements for rescue analgesia, higher caregiver satisfaction, and greater overall treatment success. Importantly, these improvements were achieved without a significant increase in adverse events, confirming that the combination regimen maintained a favorable safety profile when administered at recommended pediatric doses. The findings are consistent with current evidence supporting multimodal analgesic strategies and suggest that combined acetaminophen and ibuprofen therapy represents an effective, safe, and practical approach for treating mild to moderate acute pain in children. Wider implementation of this strategy, supported by appropriate caregiver education and adherence to standardized dosing guidelines, may improve pediatric pain management and contribute to better clinical outcomes. Further large-scale multicenter studies with longer follow-up periods are recommended to confirm these findings and evaluate the long-term safety and effectiveness of combination therapy across broader pediatric populations.

References

Kuo, N., Su, N. Y., Hou, S. K., & Kang, Y. N. (2021). Effects of acetaminophen and ibuprofen monotherapy in febrile children: a meta-analysis of randomized controlled trials. *Archives of medical science : AMS*, *18*(4), 965–981. https://doi.org/10.5114/aoms/140875

Charde, V., Sanklecha, M., Rajan, P., Sangoi, R. V., A, P., Palande, A., Dighe, P., Kothari, R., & Mittal, G. (2023). Comparing the Efficacy of Paracetamol, Ibuprofen, and a Combination of the Two Drugs in Relieving Pain and Fever in the Pediatric Age Group: A Prospective Observational Study. *Cureus*, *15*(10), e46907. https://doi.org/10.7759/cureus.46907

Pierce, C. A., & Voss, B. (2010). Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *The Annals of pharmacotherapy*, *44*(3), 489–506. https://doi.org/10.1345/aph.1M332

Harasymczuk, M., Moretti, A., Barcaroli, M., Quarchioni, E., Tulipano, A., Nicolotti, A., Procaccini, M., Salvatori, E., & Cattaneo, A. (2026). Effectiveness and Safety of the Combination of Paracetamol 1000 mg and Ibuprofen 300 mg Versus Ibuprofen 600 mg in Monotherapy in Acute Low Back Pain: Results from a Phase IV Randomized Study. *Journal of clinical medicine*, *15*(5), 2022. https://doi.org/10.3390/jcm15052022

Merry, A. F., Edwards, K. E., Ahmad, Z., Barber, C., Mahadevan, M., & Frampton, C. (2013). Randomized comparison between the combination of acetaminophen and ibuprofen and each constituent alone for analgesia following tonsillectomy in children. *Canadian journal of anaesthesia = Journal canadien d'anesthesie*, *60*(12), 1180–1189. https://doi.org/10.1007/s159-72-59-72

Paul, I. M., & Walson, P. D. (2021). Acetaminophen and ibuprofen in the treatment of pediatric fever: a narrative review. *Current medical research and opinion*, *37*(8), 1363–1375. https://doi.org/10.1080/03007995.2021.1928617

Hartling, L., Ali, S., Dryden, D. M., Chordiya, P., Johnson, D. W., Plint, A. C., Stang, A., McGrath, P. J., & Drendel, A. L. (2015). How Safe Are Common Analgesics for the Treatment of Acute Pain for Children? A Systematic Review. *Pain Research and Management*, *2016*(1), 5346819. https://doi.org/10.1155/2016/5346819

Milani, G. P., Nicolini, G., Cananzi, M., Spiezia, L., & Vidal, E. (2026). Efficacy and Safety of Paracetamol and NSAIDs for Fever and Pain Management in Children with Chronic Diseases: A Narrative Review. *Children (Basel, Switzerland)*, *13*(1), 71. https://doi.org/10.3390/children13010071

Mistry, N., & Hudak, A. (2014). Combined and alternating acetaminophen and ibuprofen therapy for febrile children. *Paediatrics & child health*, *19*(10), 531–532. https://doi.org/10.1093/pch/19.10.531

Motov, S., Butt, M., Masoudi, A., Palacios, W., Fassassi, C., Drapkin, J., Likourezos, A., Hossain, R., Brady, J., Rothberger, N., Flom, P., Zerzan, J., & Marshall, J. (2020). Comparison of Oral Ibuprofen and Acetaminophen with Either Analgesic Alone for Pediatric Emergency Department Patients with Acute Pain. *The Journal of emergency medicine*, *58*(5), 725–732. https://doi.org/10.1016/j.jemermed.2020.02.010