Original Article

Assessing the safety and adverse effects of paracetamol, ibuprofen, and their combination in paediatric pain and fever management: A prospective observational study

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Abstract

Purpose: Pain and fever are common paediatric complaints that demand meticulous symptom alleviation to ensure the child's holistic well-being. Paracetamol, ibuprofen, and their synergistic coadministration occupy a crucial position, rendering the management of these symptoms efficacious. This study aims to evaluate the safety and adverse effects of paracetamol, ibuprofen, and their combination comprehensively. **Methods:** A prospective observational study was conducted at the Department of Paediatrics, Bombay Hospital Institute of Medical Sciences, Mumbai, India. 108 paediatric patients aged 6 months to 18 years experiencing fever, pain, or both. Patients were assigned to receive one of the three medications and were randomized into one of the three groups: paracetamol, ibuprofen, or a combination. Baseline and 48-hour assessments included vital signs, adverse effects, and biochemical markers including SGOT, SGPT, serum creatinine, platelet count, and occult blood in stool samples. **Results:** Paracetamol, ibuprofen, and their combination were found to be equally effective in relieving symptoms associated with fever and pain. The most common adverse effect observed was vomiting, with minimal occurrences of rash, cough, and diarrhoea. Biochemical markers, including SGOT, SGPT, serum creatinine, platelet count, and occult blood in stool samples, remained within normal ranges after 48 h of drug administration. **Conclusion:** This study affirms the safety of paracetamol, ibuprofen, and their combination for paediatric pain and fever management. Minimal adverse effects and the absence of significant biochemical derangements support their favourable risk–benefit profiles, emphasizing their importance in paediatric clinical practice.

Keywords: Fever, ibuprofen, paediatric, pain, paracetamol

Introduction

Pain and fever are common reasons for paediatric visits in primary care, necessitating effective and safe management strategies. Paracetamol and ibuprofen, alone or combined, are widely used for symptom relief in children. These symptoms, although common, entail complex physiological processes. Pain stems from the activation of nociceptors in response to tissue damage or injury.[1,2] Fever, on the other hand, is a response orchestrated by the body to various triggers, primarily infections, inflammation, or other medical conditions. Fever enhances the

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body's immune response, making it a fundamental defence mechanism against infections. By creating an environment less favourable for the growth and replication of pathogens, the body's immune system becomes more efficient in combating the underlying cause of the fever.[3]

Although pain and fever are essential indicators of underlying health issues, effectively managing these symptoms is crucial for a patient's comfort and overall well-being. Treatment options for managing pain and fever in children are varied, with medications like paracetamol and ibuprofen serving as cornerstone therapies. Paracetamol, a centrally acting analgesic and antipyretic agent, is widely used for its efficacy in pain relief and fever reduction. The exact mechanism of its action is not fully elucidated, but it is widely believed to operate by inhibiting the synthesis of prostaglandins in the central nervous system.[4] Ibuprofen, on the other hand, belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs) and functions by inhibiting cyclooxygenase enzymes (COX), specifically COX-1 and COX-2. By blocking prostaglandin production, ibuprofen effectively reduces pain and inflammation, making it a valuable therapeutic option in pediatric care.[5]

However, despite their widespread use, challenges and risks are associated with the administration of these medications in children. Paracetamol is often the preferred choice for pain and fever management, especially in children and individuals who cannot tolerate NSAIDs due to contraindications.[6,7] Its safety profile, especially when used within recommended doses, makes it a popular option for various age groups. Paracetamol is generally well tolerated but poses risks of hepatotoxicity, particularly in cases of overdose or prolonged use. Moreover, gastrointestinal adverse effects, such as dyspepsia and nausea, may occur, especially at higher doses.[8-10] The European Medicines Agency (EMA) receives numerous adverse event reports related to paracetamol, with symptoms including nausea, vomiting, elevated liver enzyme levels, abdominal pain, hypersensitivity reactions, and skin issues.[11] Studies have shown paracetamol's association with skin hypersensitivity reactions such as angioedema, urticaria, maculopapular exanthema, and rash.[12] Similarly, ibuprofen usage has been linked to gastrointestinal complications and hypersensitivity reactions, emphasizing the importance of cautious prescribing practices in pediatric populations.[8,13,14]

The rationale for this study lies in the necessity to evaluate the safety and efficacy of paracetamol and ibuprofen, within the Indian pediatric population. Although the safety profiles of these medications are well-established globally, regional differences, including genetic variations, socioeconomic factors, and nutritional status, may influence their effects and tolerability. Notably, a prior study conducted at the Bombay Hospital Institute of Medical Sciences reaffirmed the favorable efficacy of paracetamol, ibuprofen, and their combination in addressing the prevalent pediatric complaints of fever and pain.[15] Given the crucial role of primary care physicians in pediatric care, understanding the safety and efficacy of these medications is paramount.

This study aims to build upon existing research, offering evidence-based insights to optimize pediatric care and guide clinical decision making in India. The major objective of this study was to determine the adverse effects and safety profile of paracetamol, ibuprofen, and the combination of two drugs in paediatric subjects having complaints of fever and pain.

Materials and Methods

This study used a prospective observational design to investigate the safety and efficacy of paracetamol and ibuprofen in pediatric patients presenting with fever and/or pain. The study was conducted over a duration of 24 months at the Department of Pediatrics, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India. The methodology used is summarized in Figure 1. Ethic committee was approval obtained on 12/10/21.

Study population and selection criteria

The study population comprised pediatric patients aged 6 months to 18 years who were admitted to the hospital with complaints of fever, pain, or both and for whom the use of paracetamol or ibuprofen was deemed appropriate. Patients with known allergies to paracetamol, ibuprofen, or other NSAIDs were excluded, as were those regularly taking these medications for chronic conditions. In addition, patients with significant comorbidities such as cardiovascular diseases, renal dysfunction, or endocrine disorders were excluded from the study.

Sample size determination

The study's sample size was determined using OpenEpi 3.01 statistical software from the Centers for Disease Control and Prevention in Atlanta, Georgia, USA. The calculation was based on a confidence level of 95%, a study power of 80%, and an alpha of 0.05, resulting in an estimated sample size of 98. However, to account for potential dropouts, a sample size of 108 was ultimately chosen.

Drug administration schedule

Upon admission, demographic data including age and gender were recorded for each participant. Vital signs such as temperature, heart rate, respiratory rate, and oxygen saturation were also documented. Patients were randomly assigned to one of three treatment groups: paracetamol, ibuprofen, or a combination of both. Paracetamol was administered at a dosage of 15 mg/kg/dose four times a day, while ibuprofen was given at a dosage of 10 mg/kg/dose 3 times a day. Before administering the medication, the child's baseline axillary temperature was recorded for all age groups. In children aged 6 months to 6 years, pain levels were assessed using the Face, Legs, Activity, Cry, and Controllability (FLACC) scale, whereas in those aged 6 to 18 y, the Visual Analog Scale (VAS) was used. Temperature was monitored

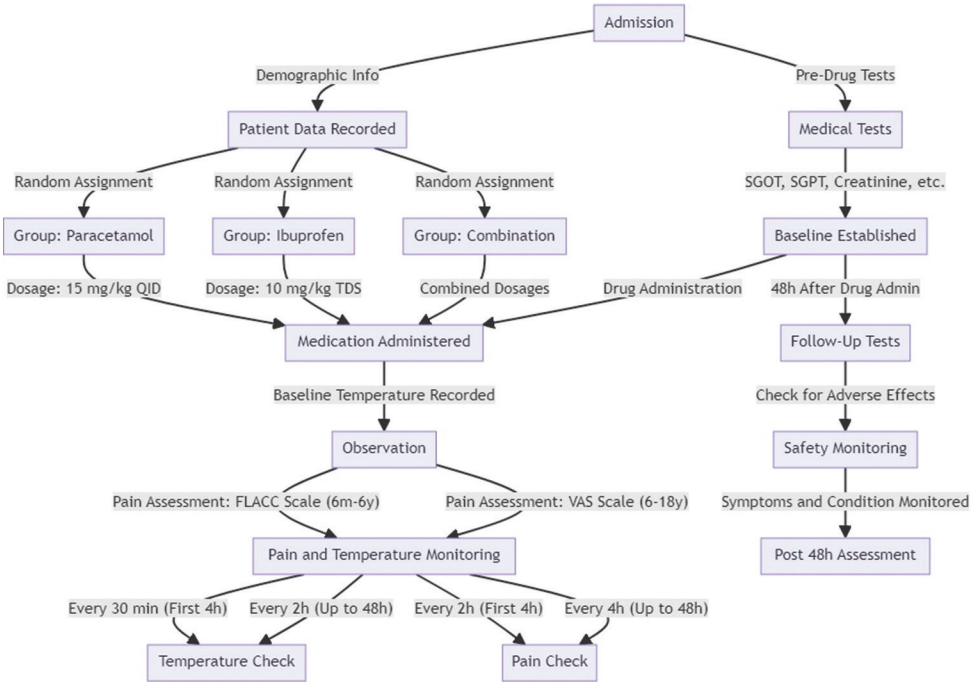

Figure 1: Methodology Diagram

every 30 min for the first 4 h and then at 2-h intervals for up to 48 h. Pain assessments were conducted every 2 h during the initial 4 h and then at 4-h intervals.

Measuring the adverse effects and safety profile

Baseline laboratory investigations including serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, platelet count, and stool occult blood analysis were performed before initiating drug therapy. These tests were repeated 48 hours after the initiation of treatment to assess any acute changes or adverse reactions. In addition, clinical symptoms and vital signs were monitored throughout the study period.

Statistical analysis

Descriptive statistics such as means, standard deviations, counts, and percentages were used to summarize the demographic and clinical characteristics of the study population. The incidence of adverse effects and changes in biochemical parameters was also analyzed using appropriate statistical methods.

Results

Demographic characteristics

A total of 108 pediatric patients, aged 6 months to 18 years, were included in the study. Table 1 displays the distribution of patients across different age categories and treatment groups. The majority of patients (71.3%) fell within the age group of 6 months to <5 years, with 27 patients receiving paracetamol, 23 receiving ibuprofen, and 27 receiving a combination of both drugs. Males outnumbered females across all treatment groups, consistent with the overall gender distribution in the study population.

Table 1: Distribution of patients by age category and treatment group

Age category	Paracetamol	Ibuprofen	Paracetamol and ibuprofen	Total
6 mo-<5 y	27	23	27	77
5-10 y	6	7	6	19
>10 y	3	6	3	12
Total	36	36	36	108

Efficacy in Relieving Symptoms: The efficacy of paracetamol, ibuprofen, and their combination in relieving fever and pain-associated symptoms was assessed upon admission (0 hours) and after 48 hours of drug administration. Table 2 presents the distribution of symptoms at 0 hours, categorized by drug administered. Across all treatment groups, the majority of patients exhibited discomfort, reduced activity levels, decreased appetite, and disturbed sleep upon admission.

At 48 hours postadministration, a significant improvement in symptoms was observed across all treatment groups. Table 3 illustrates the distribution of symptoms at 48 hours, indicating a normalization of discomfort, activity levels, appetite, and sleep patterns in the majority of patients.

Overall, paracetamol, ibuprofen, and their combination demonstrated similar efficacy in alleviating fever and pain-associated symptoms, with a notable improvement observed after 48 hours of drug administration.

Adverse effects

The incidence of adverse effects associated with paracetamol, ibuprofen, and their combination was assessed during the study

Table 2: Distribution of symptoms at 0 hours by drug administered

Symptom	Paracetamol	Ibuprofen	Paracetamol and ibuprofen
Discomfort			
Normal	18 (50.0%)	16 (44.4%)	13 (36.1%)
Not quite normal	15 (41.7%)	11 (30.6%)	18 (50.0%)
Some pain or distress	3 (8.3%)	9 (25.0%)	5 (13.9%)
Crying or very distressed	0 (0.0%)	0 (0.0%)	0 (0.0%)
Activity			
Normal	22 (61.1%)	25 (69.4%)	22 (61.1%)
Quiet for longer than usual	12 (33.3%)	11 (30.6%)	12 (33.3%)
Hardly moving about	2 (5.6%)	0 (0.0%)	2 (5.6%)
Not moving about willingly	0 (0.0%)	0 (0.0%)	0 (0.0%)
Appetite			
Normal	18 (50.0%)	25 (69.4%)	20 (55.6%)
Eating less than normal	12 (33.3%)	9 (25.0%)	13 (36.1%)
Eating much less than normal	6 (16.7%)	2 (5.6%)	3 (8.3%)
Vomiting or refusing food or drink	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sleep			
Normal	19 (52.8%)	26 (72.2%)	23 (63.9%)
More than usual	13 (36.1%)	10 (27.8%)	10 (27.8%)
More disturbed than usual	4 (11.1%)	0 (0.0%)	3 (8.3%)
A lot more disturbed than usual	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3: Distribution of symptoms at 48 hours by drug administered

Symptom	Paracetamol	Ibuprofen	Paracetamol and ibuprofen
Discomfort			
Normal	32 (88.9%)	34 (94.4%)	33 (91.7%)
Not quite normal	4 (11.1%)	2 (5.6%)	3 (8.3%)
Some pain or distress	0 (0.0%)	0 (0.0%)	0 (0.0%)
Crying or very distressed	0 (0.0%)	0 (0.0%)	0 (0.0%)
Activity			
Normal	29 (80.6%)	30 (83.3%)	33 (91.7%)
Quiet for longer than usual	7 (19.4%)	6 (16.7%)	3 (8.3%)
Hardly moving about	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not moving about willingly	0 (0.0%)	0 (0.0%)	0 (0.0%)
Appetite			
Normal	25 (69.4%)	26 (72.2%)	27 (75.0%)
Eating less than normal	10 (27.8%)	10 (27.8%)	9 (25.0%)
Eating much less than normal	1 (2.8%)	0 (0.0%)	0 (0.0%)
Vomiting or refusing food or drink	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sleep			
Normal	26 (72.2%)	34 (94.4%)	32 (88.9%)
More than usual	10 (27.8%)	2 (5.6%)	4 (11.1%)
More disturbed than usual	0 (0.0%)	0 (0.0%)	0 (0.0%)
A lot more disturbed than usual	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4: Distribution of adverse effects by drug administered

Adverse effect	Paracetamol	Ibuprofen	Paracetamol and ibuprofen
None	29 (80.6%)	30 (83.3%)	26 (72.2%)
Vomiting	5 (13.9%)	3 (8.3%)	4 (11.1%)
Rash	0 (0.0%)	2 (5.6%)	3 (8.3%)
Cough	0 (0.0%)	1 (2.8%)	1 (2.8%)
Diarrhea	2 (5.6%)	0 (0.0%)	1 (2.8%)
Others	0 (0.0%)	0 (0.0%)	1 (2.8%)

period. Table 4 outlines the distribution of adverse effects by drug administered. Across all treatment groups, the majority of patients experienced no adverse effects. Vomiting was the most common side effect reported, followed by rash and cough. Notably, the combination of paracetamol and ibuprofen exhibited slightly higher rates of adverse effects compared to either drug used alone.

These findings highlight the generally favorable safety profile of paracetamol and ibuprofen in pediatric patients, with vomiting being the most commonly reported adverse effect.

Biochemical parameters

Changes in biochemical parameters, including platelet count and serum levels of SGOT, SGPT, and creatinine, were evaluated before and after 48 hours of drug administration. Table 5 presents the mean values and standard deviations of these parameters across the three treatment groups at 0 hours and 48 hours.

Table 6 presents the presence of occult blood in stool samples collected before (0 hours) and after (48 hours) drug administration across the three treatment groups. The majority of patients tested positive for occult blood at baseline, with a slight decrease in positivity rates observed after 48 hours, indicating minimal gastrointestinal bleeding or mucosal injury associated with paracetamol or ibuprofen use.

Notably, there were no significant changes in platelet count or serum enzyme levels observed across any of the treatment groups after 48 hours of drug administration. In addition, stool occult blood analysis revealed minimal instances of occult blood positivity post-treatment, indicating the absence of significant gastrointestinal bleeding or mucosal injury associated with paracetamol or ibuprofen use in the study population.

Top of Form

Discussion

For primary care physicians, having safe and efficacious treatment options for paediatric pain and fever management is paramount. Paracetamol and ibuprofen, as well as their combination, offer primary care providers versatile tools to address these common complaints in children. The comparable effectiveness of these medications underscores the importance of individualizing treatment based on patient needs and preferences, a principle fundamental to primary care practice.

In primary care settings, where comprehensive patient care is the norm, the findings of this study provide reassurance to physicians regarding the safety and efficacy of paracetamol, ibuprofen, and combination therapy for paediatric pain and fever management. By incorporating these findings into clinical practice, primary care physicians can confidently navigate the complexities of managing these symptoms in paediatric patients, promoting their overall well-being and satisfaction.

Our results indicate that paracetamol, ibuprofen, and their combination exhibited comparable efficacy in relieving fever and pain-associated symptoms in pediatric patients. This aligns with previous research suggesting that both paracetamol and ibuprofen are effective in managing pain and fever in children.[15-18] The observed improvement in symptoms over the 48-hour study period underscores the therapeutic benefits of these medications in providing symptomatic relief.

The safety profile of paracetamol and ibuprofen is a critical consideration in pediatric patient care. Our study found that the incidence of adverse effects was generally low across all treatment groups, with vomiting being the most commonly reported side effect. This finding is consistent with existing literature, which highlights vomiting as a common adverse event associated with the use of these medications in children.[18-20] In the paracetamol group, 13.9% of cases experienced vomiting, followed by 5.6% encountering diarrhoea. Contrastingly, the ibuprofen group recorded vomiting as the primary side effect in 8.3% of cases, accompanied by rash (5.6%) and cough (2.8%). Intriguingly, the combination of paracetamol and ibuprofen group reported vomiting as the leading side effect (11.1%), trailed by a rash (8.3%), and isolated instances of cough, diarrhoea, and other effects (each accounting for 1%). These findings harmonized remarkably well with analogous observations in studies by Lanza FL *et al.*,[21] Ivey KJ,[22] Abramson SB,[23] Sanchez B *et al.*,[24] Simons F *et al.*,[25] and the European Medicines Agency 2017 Annual report on Eudra Vigilance.[26] Furthermore, our findings underscored vomiting as the paramount side effect across all three groups: paracetamol (13.9%), paracetamol and ibuprofen (11.1%), and ibuprofen (8.3%). Notably, this alignment was consistent with outcomes elucidated in a few studies.[18,20]

The manifestation of rash as an adverse effect was most conspicuous in the paracetamol and ibuprofen groups (8.3%),

Table 5: Changes in biochemical parameters before and after drug administration

Parameter	Paracetamol (0 h)	Paracetamol (48 h)	Ibuprofen (0 h)	Ibuprofen (48 h)	Paracetamol and ibuprofen (0 h)	Paracetamol and ibuprofen (48 h)
Platelet count (×10^5)	3.94±2.12	3.68±1.89	3.29±1.20	3.14±1.25	3.39±1.47	3.41±1.48
SGOT (U/L)	37.72±20.34	39.81±21.89	54.00±58.99	47.69±31.60	38.69±11.76	41.47±24.54
SGPT (U/L)	35.89±21.83	36.39±21.91	42.64±31.15	44.69±37.62	31.72±11.79	30.50±11.59
Creatinine (mg/dL)	0.47±0.20	0.44±0.20	0.50±0.14	0.42±0.13	0.48±0.15	0.40±0.15

Table 6: Effect on stool for occult blood

Stool for occult blood	Paracetamol (0 h)	Paracetamol (48 h)	Ibuprofen (0 h)	Ibuprofen (48 h)	Paracetamol and ibuprofen (0 h)	Paracetamol and ibuprofen (48 h)
Positive (1)	21 (75.0%)	16 (59.3%)	26 (86.7%)	25 (86.2%)	19 (67.9%)	14 (56.0%)
Negative (2)	7 (25.0%)	11 (40.7%)	4 (13.3%)	4 (13.8%)	9 (32.1%)	11 (44.0%)

followed closely by the ibuprofen group (5.6%). Astonishingly, the paracetamol group exhibited no instances of rash, mirroring congruent findings in studies by Sanchez M *et al.*[25] Cough, as an adverse effect, made a minimal impact, being observed solely in the combination group and the ibuprofen group (both at 2.8%). Notably, the paracetamol group remained unscathed by cough-related adverse events, rendering it insignificant in our study cohort. Diarrhoea, while relatively infrequent, was predominantly noted in the paracetamol group (5.6%), with an isolated case in the combination group. Strikingly, no instances of diarrhoea were reported in the ibuprofen group, a phenomenon that resonated with observations in studies by Bjarnason *et al.*[27] and Davies *et al.*[28] However, it is pertinent to acknowledge that the study by Morgan *et al.*[29] presented subtly differing results.

It is essential to recognize the distinct mechanisms of action between paracetamol and ibuprofen, as depicted in Figure 2. The precise mechanism of paracetamol remains uncertain; however, it is believed to involve the inhibition of COX-3 centrally, thereby impeding prostaglandin synthesis within the central nervous system. Conversely, ibuprofen functions peripherally by inhibiting cyclooxygenase enzymes, thereby diminishing prostaglandin production at the site of inflammation.[4,5]

Assessing changes in biochemical parameters is essential for monitoring the potential adverse effects of medications. Our study revealed no significant alterations in platelet count or serum enzyme levels after the administration of paracetamol, ibuprofen, or their combination. These findings are consistent with previous research indicating that these drugs are generally well-tolerated and do not cause significant hematological or hepatic toxicity in pediatric patients.[30,31] In addition, the absence of occult blood positivity in stool samples suggests minimal gastrointestinal mucosal injury associated with the use of these medications.

Limitations and future directions

Despite the valuable insights provided by this study, several limitations must be acknowledged. First, the lack of a placebo control group limits our ability to assess the true efficacy of the medications studied. In addition, the short-term nature of the study may not capture potential long-term adverse effects associated with prolonged medication use.

Another limitation is the omission of investigating the underlying causes of fever or pain in the subjects, as well as the medications used to address these underlying conditions. The study did not delve into the interactions between these medications and the drugs being studied, namely, paracetamol and ibuprofen. Understanding these potential interactions could have provided a more comprehensive perspective on the safety and efficacy of the medications in pediatric patients.

Furthermore, the study design focused primarily on the immediate symptomatic relief provided by paracetamol, ibuprofen, and their combination. Future research should consider exploring the long-term effects and outcomes associated with these medications, as well as their impact on overall patient health and quality of life.

Lastly, the study was conducted in a single center, which may limit the generalizability of the findings to broader populations. Future studies should aim to replicate these findings in diverse patient populations and clinical settings to ensure the robustness and applicability of the results.

Future research should focus on addressing these limitations and further elucidating the safety and efficacy profiles of paracetamol, ibuprofen, and their combination in pediatric patients.

Conclusion

In summation, our study provides compelling evidence affirming the safety profile of paracetamol, ibuprofen, and their combination. The absence of substantial adverse effects and biochemical derangements, even after round-the-clock administration for 48 h, underscores the favourable risk–benefit ratio of these medications. However, while this study provides crucial insights into the safety aspects, it is also essential to remember that correct dosing and adherence to recommended

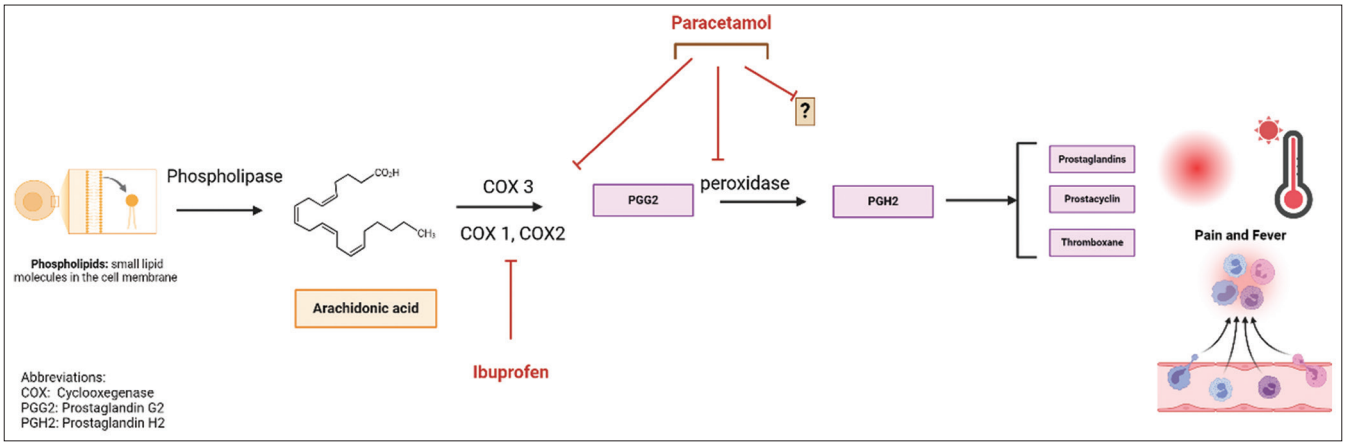

Figure 2: Mechanism of action of Paracetamol and Ibuprofen

guidelines remain imperative to ensuring the safe and effective use of these medications. Future research should continue to explore their long-term safety and efficacy to further enhance our understanding and confidence in their clinical utility.

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Conflicts of interest

There are no conflicts of interest.

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