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Original Article

Short-Term Safety and Adverse-Event Profile of Postoperative Rectal Diclofenac, Rectal Paracetamol, and Their Combination in Pediatric Elective Surgery: A Randomized Double-Blind Study

Dr. Chavadi Vivek Manohar[1], Dr. Roopadevi Hosamani[2], Dr. Farha Deeba Rajasab[3]

1 Assistant Professor, Department of Anesthesiology, Haveri Institute of Medical Sciences, Haveri, Karnataka, India.

2 Consultant Radiologist, Shree Scan Centre, Haveri, Karnataka, India.

3 Associate Professor, Shri Atal Bihari Vajpayee Medical College and Research Institute, Bengaluru, Karnataka, India.

Corresponding Author:
Dr. Chavadi Vivek Manohar

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ABSTRACT

The perioperative use of rectal paracetamol and diclofenac is common in children, but direct comparative data on short-term postoperative adverse events remain limited. This randomized, double-blind study included 90 children aged 2-14 years with American Society of Anesthesiologists physical status I-II undergoing elective surgery. Participants were allocated equally to rectal paracetamol 40 mg/kg (Group P), rectal diclofenac 1 mg/kg (Group D), or both drugs at the same doses (Group PD). Nausea, vomiting, pruritus, and respiratory difficulty were recorded during the 6-hour postoperative observation period. Because the source study did not include formal causality adjudication, these outcomes were treated as adverse events rather than confirmed adverse drug reactions. Nausea occurred in 18/30 (60.0%) patients in Group P, 8/30 (26.7%) in Group D, and 6/30 (20.0%) in Group PD; the intergroup distribution was significant (exact P=0.003). Pruritus occurred in 3/30 (10.0%), 2/30 (6.7%), and 1/30 (3.3%) patients, respectively (exact P=0.868). Vomiting was reported in 5/30 (16.7%), 3/30 (10.0%), and 3/30 (10.0%) patients, respectively (exact P=0.780). No respiratory difficulty was recorded in any group. The three regimens were associated mainly with mild, short-term postoperative events. Nausea was more frequent in the paracetamol-only group, whereas vomiting and pruritus did not differ significantly. These findings should be interpreted cautiously because all patients received standardized anesthesia, ondansetron, and perioperative tramadol, and the study was not powered to detect rare or delayed adverse drug reactions.

Keywords: adverse drug reaction; adverse event; diclofenac; paracetamol; pediatric anesthesia; postoperative nausea and vomiting; rectal suppository; drug safety.

INTRODUCTION

Medication safety is a central consideration in pediatric perioperative care because children differ from adults in drug disposition, communication of symptoms, and vulnerability to dosing errors. Postoperative symptoms such as nausea, vomiting, pruritus, and respiratory disturbance may delay recovery and cause substantial distress to children and caregivers. Their interpretation is often difficult, however, because the same symptoms may arise from anesthetic agents, opioids, the surgical procedure, or the non-opioid analgesic regimen itself [1].

Paracetamol and diclofenac are widely used non-opioid medicines in pediatric surgical practice. Paracetamol is generally well tolerated at therapeutic doses, but dose-related hepatic toxicity remains an important concern. Diclofenac, a non-steroidal anti-inflammatory drug, may be associated with gastrointestinal irritation, renal impairment, altered platelet function, hypersensitivity, and bronchospasm in susceptible patients. These risks are strongly influenced by dose, duration of exposure, comorbidity, hydration status, and concomitant medication. In selected pediatric surgical populations, rectal diclofenac and paracetamol have been used without a clear increase in major perioperative complications, although the available safety evidence is less extensive than the evidence addressing pain outcomes [2-6].
The rectal route is useful when oral medication is unsuitable, but it also introduces route-specific considerations, including local irritation and variable absorption. Previous pediatric studies of rectal diclofenac, rectal paracetamol, or their combination have generally reported comparable adverse-event rates between treatment groups; nevertheless, individual trials were usually designed primarily around analgesic outcomes and were not powered to detect uncommon adverse reactions [7-9].

The present safety-focused analysis used data from a randomized three-arm study of pediatric elective surgery. Its objective was to compare the short-term postoperative adverse-event profile of rectal paracetamol, rectal diclofenac, and combination therapy.

MATERIALS AND METHODS

Study design and setting

This randomized, double-blind, controlled clinical study was conducted in the Department of Anaesthesia, Navodaya Medical College, Hospital and Research Centre, Raichur, India, from June 2012 to June 2014. Institutional ethics approval was obtained before recruitment, and written informed consent was obtained before enrollment. The present Study is a secondary safety analysis of the trial and does not report the analgesic efficacy outcomes.

Participants

Ninety children of either sex, aged 2-14 years, with American Society of Anesthesiologists (ASA) physical status I or II and scheduled for elective surgery were included. Exclusion criteria were ASA physical status III or IV, bronchial asthma, renal or hepatic disease, prolonged bleeding or clotting time, known allergy to either study medicine, and anorectal anomaly. These exclusions created a lower-risk study population and should be considered when interpreting safety generalizability.

Randomization and interventions

Participants were randomly allocated to three equal groups of 30 patients. Group P received rectal paracetamol 40 mg/kg, Group D received rectal diclofenac 1 mg/kg, and Group PD received rectal paracetamol 40 mg/kg plus rectal diclofenac 1 mg/kg. The study medications were administered after induction of general anesthesia and endotracheal intubation according to the source protocol.

Standardized perioperative management

All patients received standardized perioperative management. Oral triclofos 100 mg/kg was used as preoperative premedication. Intravenous glycopyrrolate 0.004 mg/kg and ondansetron 0.1 mg/kg were given before induction. General anesthesia was induced with intravenous tramadol 2 mg/kg and propofol 1-2.5 mg/kg, followed by atracurium 0.5 mg/kg and endotracheal intubation. Anesthesia was maintained with halothane, nitrous oxide, oxygen, and intermittent atracurium. Additional intravenous tramadol was titrated to hemodynamic response. Non-invasive blood pressure, electrocardiography, end-tidal carbon dioxide, and peripheral oxygen saturation were monitored.

Safety outcomes

During the 6-hour postoperative observation period, the occurrence of nausea, vomiting, pruritus, and respiratory difficulty was recorded in each group. The source dataset did not provide severity grading, time of onset, duration, treatment required, dechallenge/rechallenge information, or formal causality assessment. Consequently, the recorded symptoms are described as postoperative adverse events and potential adverse drug reactions, not as confirmed reactions attributable to paracetamol or diclofenac. The source data did not systematically report renal, hepatic, gastrointestinal bleeding, surgical bleeding, or local rectal outcomes; these endpoints were therefore not inferred or analyzed.

Statistical analysis

Categorical safety outcomes are presented as number and percentage. For this safety-focused reanalysis, the reported group counts were compared using the Fisher-Freeman-Halton exact test for 3 x 2 contingency tables because several expected cell counts were small. A two-sided P value <0.05 was considered statistically significant. Respiratory difficulty could not be statistically compared because no event occurred in any group. The original dataset did not identify whether individual patients experienced more than one event; therefore, a valid composite incidence of 'any adverse event' could not be calculated.

RESULTS

Participant characteristics:

All 90 enrolled patients were included in the safety analysis, with 30 patients in each treatment group. The groups were comparable in age, sex distribution, ASA physical status, body weight, and duration of surgery.

Table 1: Age distribution of patients studied

	Group P		Group D		Group PD	
Age in years	No	%	No	%	No	%
2 to 4	7	23.33	7	23.33	7	26.67
4 to 6	6	20	5	16.66	2	16.67
6 to 8	7	23.33	6	20	1	20
8 to 10	4	13.33	5	16.6	2	10
10 to 12	4	13.33	5	16.7	1	13.33
12 to 14	2	6.68	2	6.66	2	13.33
Total	30	100	30	100	30	100
Mean ±SD	7.33±3.45		7.53±3.52		7.43±3.75	

Samples were age matched with P=0.97

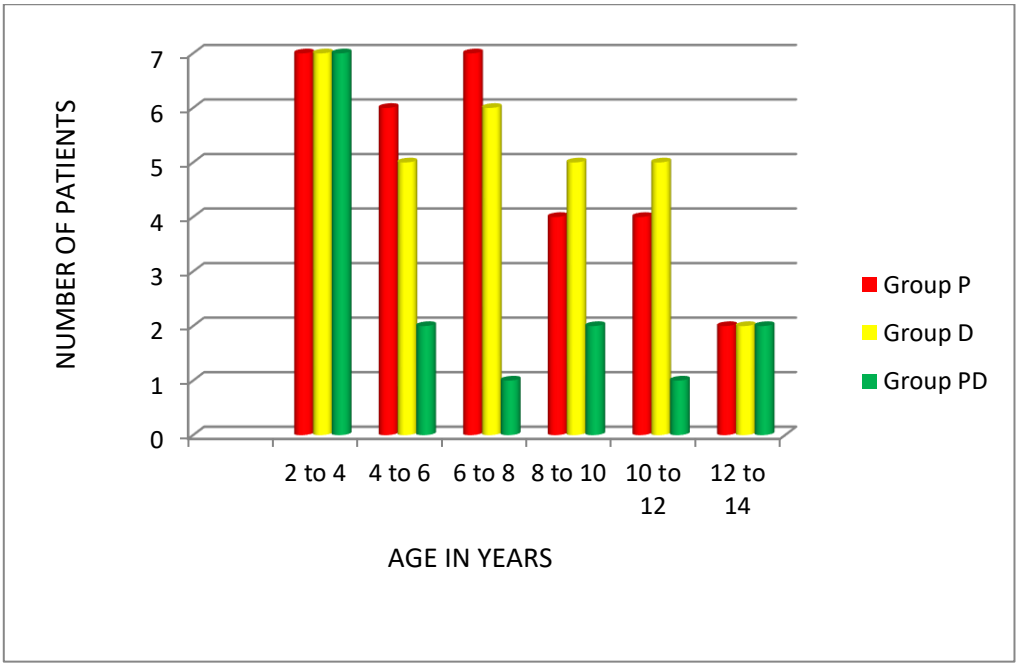

Fig1: Age distribution of patients studied

TABLE 2 Gender distribution of patients studied

	Group P		Group D		Group PD	
Gender	No	%	No	%	No	%
Male	16	50	15	50	15	50
Female	14	50	15	50	15	50
Total	30	100	30	100	30	100

Samples were gender matched with p=0.957

The study population had an even distribution with respect to gender in all three groups.

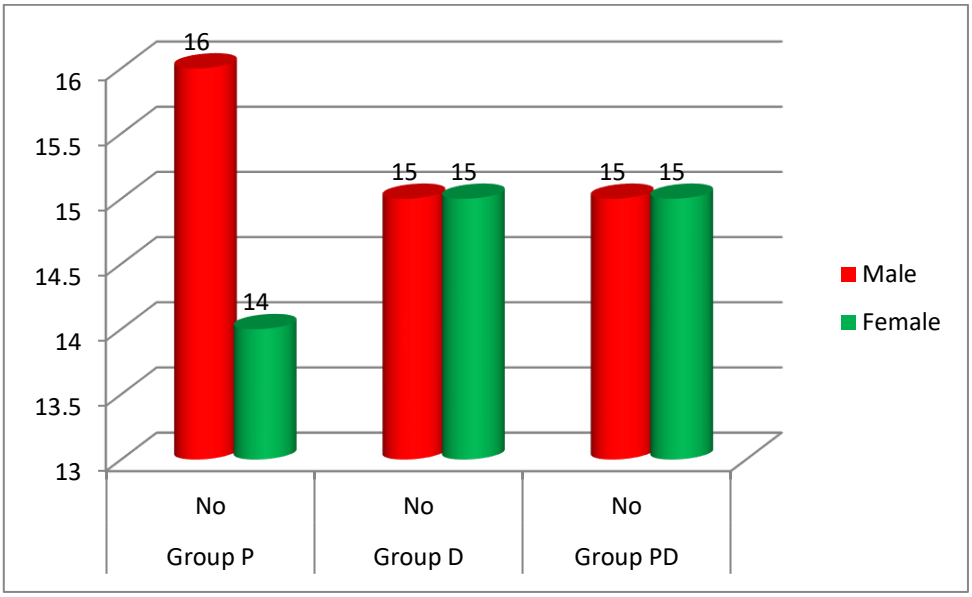

Fig 2: Gender distribution of the patients studied

Table 3: ASA-PS distribution of patients studied

ASA-PS	Group P		Group D		Group PD	
	No	%	No	%	No	%
I	13	43.3	14	46.7	14	46.7
II	17	56.7	16	53.3	16	53.3
Total	30	100.0	30	100.0	30	100.0

ASA-PS distribution was statistically similar in two groups with P=0.956

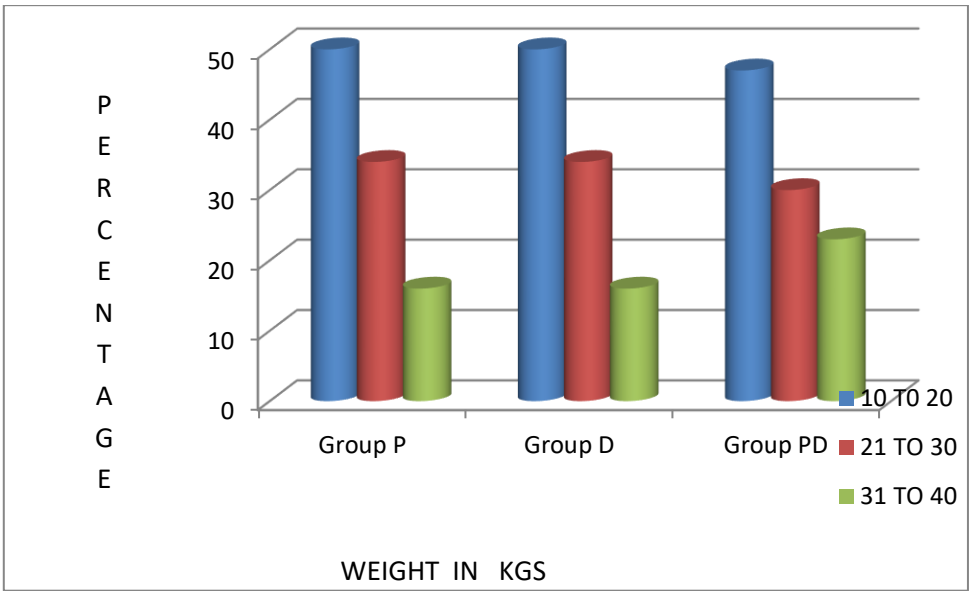

Fig 3: Weight distribution of patients studied

Postoperative adverse events:

Nausea was the most frequently recorded event. It occurred in 18 patients (60.0%) in Group P, 8 (26.7%) in Group D, and 6 (20.0%) in Group PD. The overall distribution differed significantly among the groups (exact P=0.003). The data establish an intergroup difference but, in the absence of formal causality assessment and because all patients received multiple perioperative medicines, they do not demonstrate that paracetamol directly caused nausea.

Pruritus occurred in 3 patients (10.0%) in Group P, 2 (6.7%) in Group D, and 1 (3.3%) in Group PD; the difference was not statistically significant (exact P=0.868). Vomiting was reported in 5 patients (16.7%) in Group P and 3 patients (10.0%) in each of Groups D and PD, with no significant intergroup difference (exact P=0.780). No respiratory difficulty was recorded in any of the 90 participants.

Comparative Side effects in three groups of patients studied

Table 4 : Nausea

Side effects	Group P (n=30)	Group D (n=30)	Group PD (n=30)
Nausea	60%	26.66%	20%

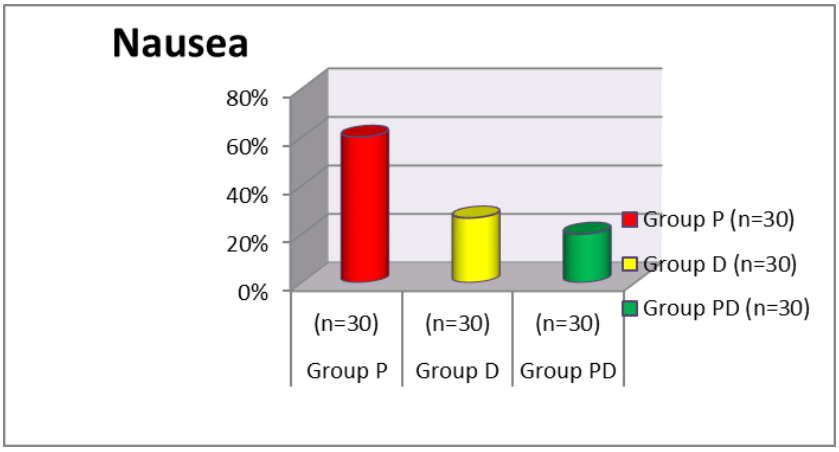

Fig 4 : Nausea

Table 5: Pruritus

Side effects	Group P (n=30)	Group D (n=30)	Group PD (n=30)
Pruritus	10.00%	6.70%	3.33%

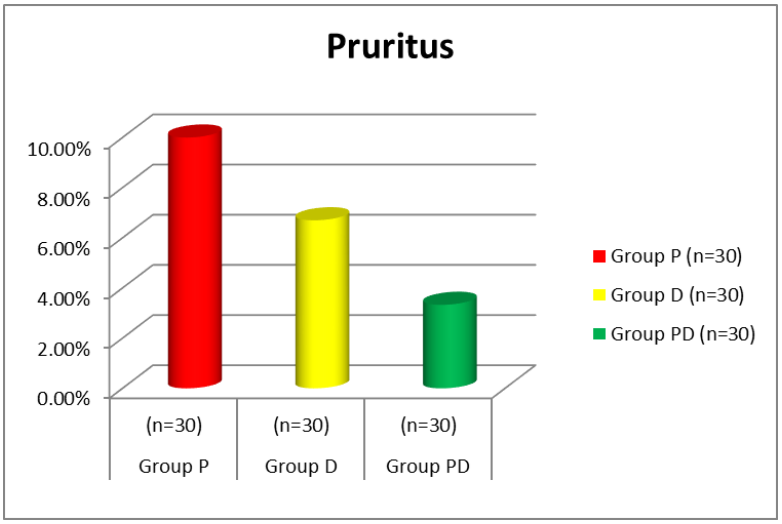

Fig 5: Pruritus

Table 6: vomiting

Side effects	Group P (n=30)	Group D (n=30)	Group PD (n=30)
Vomiting	16.66%	10.00%	10.00%

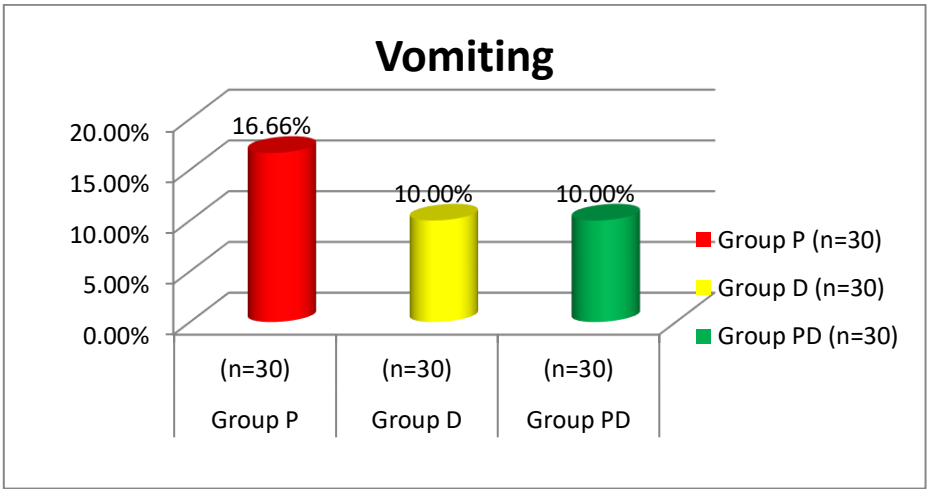

Fig 6: vomiting

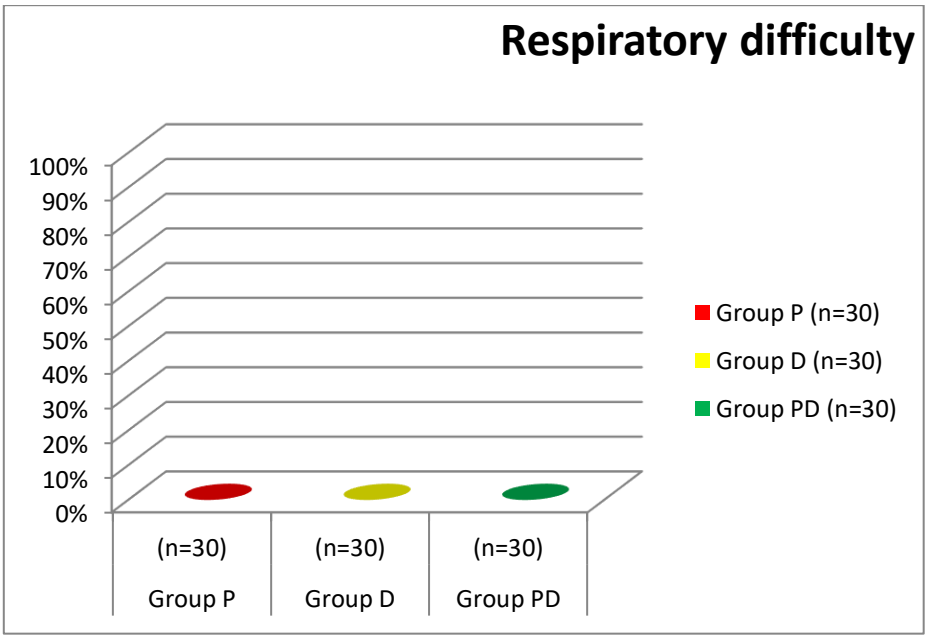

Fig 7: Respiratory difficulty

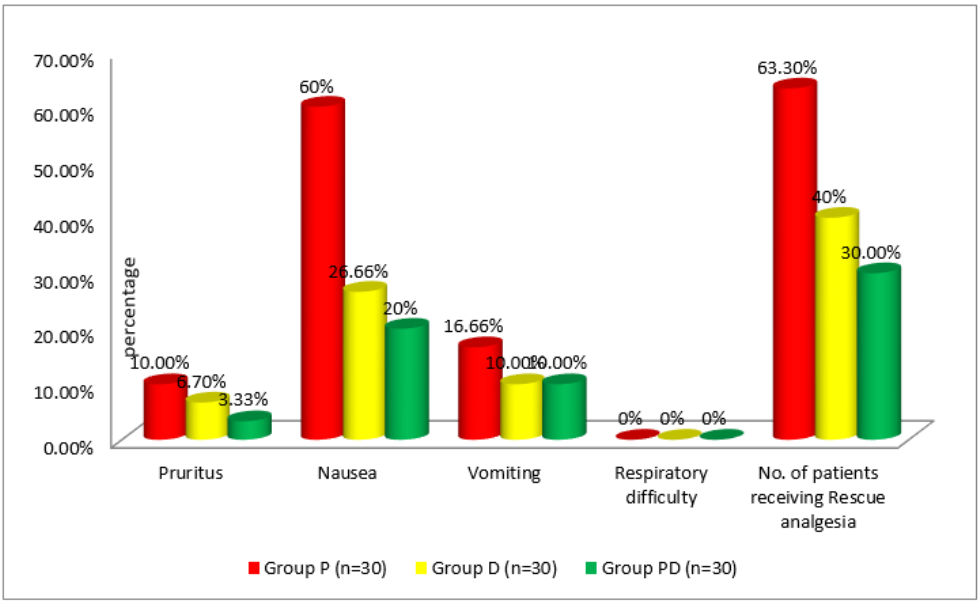

Fig8: Comparative Side effects in three groups of patients studied

DISCUSSION

This safety-focused analysis found that the three rectal regimens were associated predominantly with mild postoperative symptoms during the first 6 hours after surgery. Nausea differed significantly among the groups and was descriptively most frequent in the paracetamol-only group. By contrast, pruritus and vomiting were uncommon and showed no statistically significant intergroup differences. No respiratory difficulty was recorded.

The higher frequency of nausea in Group P should not be interpreted as evidence of a direct paracetamol adverse drug reaction. Postoperative nausea is multifactorial and may be influenced by patient age, the type and duration of surgery, inhalational anesthesia, nitrous oxide, perioperative opioids, hydration, and individual susceptibility. Every participant in this study received tramadol, halothane, nitrous oxide, and prophylactic ondansetron. These concomitant exposures make drug-specific attribution difficult. A meta-analysis by Remy et al. similarly showed that adding acetaminophen to morphine reduced opioid consumption but did not consistently reduce opioid-related nausea, vomiting, pruritus, sedation, urinary retention, or respiratory depression [9].

The absence of a significant difference in vomiting is consistent with pediatric trials in which adverse effects were comparable after paracetamol, diclofenac, or their combination. Morton and O'Brien reported comparable adverse effects across four postoperative regimens in children receiving patient-controlled morphine [8]. Mireskandari and Makarem likewise found no meaningful difference in adverse effects among children receiving rectal acetaminophen, diclofenac, their combination, or placebo after cleft palate repair [10]. Differences between studies may reflect the surgical population, background anesthesia, antiemetic use, drug timing, repeated dosing, and duration of surveillance.

Pruritus occurred in only six patients overall and was not significantly associated with treatment group. Pruritus is a recognized opioid-related postoperative symptom and may also occur with hypersensitivity, skin contact, or other perioperative exposures. Because the source study did not document rash, temporal relationship to drug administration, treatment response, or formal causality scoring, these episodes cannot be classified as confirmed reactions to paracetamol or diclofenac.

No respiratory difficulty was observed. This is reassuring within the monitored cohort but must be interpreted in light of the exclusion of children with bronchial asthma. Short et al. found no clinically important bronchospasm after a single therapeutic dose of diclofenac in 70 children with asthma [3], and a prospective pediatric pharmacovigilance study also reported a low incidence of serious diclofenac reactions [11]. Nevertheless, the present study cannot establish safety in children with asthma, active airway disease, or previous NSAID hypersensitivity because these groups were not represented.

Potential NSAID-related bleeding is another important safety consideration. Selected pediatric studies have not demonstrated clinically important deterioration in clot strength or an obvious increase in postoperative hemorrhage after diclofenac [4-6]. However, the current dataset did not provide systematic information on surgical bleeding, reoperation, gastrointestinal bleeding, platelet function, renal function, or liver biochemistry. The absence of these outcomes in the dataset should not be interpreted as evidence that the events did not occur.

The rectal route itself may cause local irritation. Standing et al. identified rectal irritation and diarrhea as uncommon probable diclofenac reactions in a prospective pediatric observational study [11]. Local rectal symptoms were not reported in the present dataset. Future trials should use a predefined safety checklist that includes local discomfort, diarrhea, abdominal pain, rash, wheezing, bleeding, urine output, and clinically indicated laboratory testing.

This study has several limitations. The sample size was modest and was calculated for the parent trial rather than for safety outcomes, making the analysis underpowered for uncommon or serious reactions. Surveillance was limited to 6 hours and could not capture delayed hepatic, renal, gastrointestinal, hypersensitivity, or bleeding events. Event severity, onset, duration, treatment, and outcome were not documented. Formal causality assessment was not performed, and multiple anesthetic and analgesic agents were administered concurrently. In addition, asthma, renal or hepatic disease, abnormal coagulation, drug allergy, and anorectal anomaly were exclusion criteria; therefore, the findings apply only to a selected lower-risk pediatric population.

Despite these limitations, the study contributes comparative descriptive data on common early postoperative symptoms after three rectal regimens. The significant difference in nausea warrants confirmation in a study specifically designed for safety, using standardized adverse-event definitions, prospective causality assessment, longer follow-up, and adequate power for uncommon events.

CONCLUSION

Within the 6-hour postoperative observation period, rectal paracetamol, rectal diclofenac, and their combination were associated mainly with mild adverse events in a selected group of ASA I-II children. Nausea differed significantly among

the treatment groups and was most frequent in the paracetamol-only group, whereas vomiting and pruritus did not differ significantly. No respiratory difficulty was observed. Because formal causality assessment was not performed and all patients received multiple perioperative medications, the recorded symptoms should be interpreted as adverse events rather than confirmed adverse drug reactions. Larger safety-focused studies with longer follow-up and systematic monitoring of bleeding, renal, hepatic, hypersensitivity, and local rectal outcomes are required.

DECLARATIONS

Funding: None.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: The study was conducted in accordance with applicable ethical standards and approved by the appropriate ethics committee where required.

Informed Consent: Informed consent was obtained from all participants involved in the study where applicable.

Author Contributions: All authors contributed to the study conception, design, data collection, analysis, manuscript preparation, and approved the final version of the manuscript.

Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request..

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