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THE COMPARISON OF STEROID, NSAID, AND COMBINATION OF STEROID NSAID ON ANALGESIA AND INFLAMMATION IN PATIENT AFTER CHOLECYSTECTOMY SURGERY: RANDOMIZED CONTROLLED TRIAL

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ABSTRACT
Postoperative pain and inflammation remain major concerns following cholecystectomy. Although paracetamol, non-steroidal anti-inflammatory drugs, and corticosteroids are widely used, the most effective regimen for superior analgesia and anti-inflammatory control is still under debate. This study aimed to assess the effect of combining paracetamol, ibuprofen, and dexamethasone compared with single or dual regimens on postoperative pain and inflammatory markers. A randomized, double-blind, controlled trial was performed at RSUD Prof. Dr. Margono Soekarjo. Forty-five patients undergoing elective open cholecystectomy were randomized into three groups: Group A (paracetamol + dexamethasone), Group B (paracetamol + ibuprofen), and Group C (paracetamol + ibuprofen + dexamethasone). Serum interleukin-6 (IL-6) and prostaglandin E2 (PGE2) were measured pre- and post-intervention, and postoperative pain was evaluated with the Numeric Rating Scale (NRS). Statistical analysis was performed using IBM SPSS version 29.0, with significance set at $p < 0.05$. Baseline demographics were similar across groups ($p > 0.05$). Group C demonstrated the greatest IL-6 reduction ($p = 0.047$), while Group B showed an increase ($p = 0.027$) and Group A no significant change ($p = 0.053$). PGE2 levels were lowest in Group C, though intra-group differences were not significant. Postoperative NRS scores varied significantly ($p < 0.001$), with Group C reporting the lowest median score compared with Groups A and B. The combination of paracetamol, ibuprofen, and dexamethasone offers superior analgesia and greater reduction in IL-6 levels compared with single or dual regimens, supporting its role as an effective multimodal analgesic strategy after cholecystectomy.

KEYWORDS: Cholecystectomy, multimodal analgesia, dexamethasone, ibuprofen, interleukin-6

INTRODUCTION
Gallstone disease is one of the most prevalent gastrointestinal disorders worldwide, and cholecystectomy remains the definitive treatment for symptomatic cases [1]. Despite its effectiveness in relieving biliary colic, postoperative pain and long-term complications remain important concerns. Postoperative pain following cholecystectomy is often underestimated and inadequately managed, yet it plays a crucial role in recovery by influencing pulmonary function, increasing morbidity, and prolonging hospital stay [2]. Open cholecystectomy, still widely performed in many developing countries due to limited access to laparoscopic equipment and expertise, is particularly associated with more severe pain and systemic inflammatory response compared to the laparoscopic approach [3]. Persistent pain after cholecystectomy is not uncommon, with reports indicating that up to 40% of patients experience recurrent or ongoing abdominal discomfort. This condition, often categorized under post-cholecystectomy syndrome, has a wide incidence range from 10% to 40% and may persist for months or even years after surgery [4], [5]. The pathogenesis is multifactorial, including surgical complications, residual or recurrent stones, sphincter of Oddi dysfunction, altered bile acid metabolism, and psychosomatic factors[6]. In addition, poorly controlled postoperative pain has been strongly associated with reduced quality of life, impaired pulmonary mechanics, psychological distress, and increased risk of chronic pain syndromes [6], [7].
Effective pain management is therefore a cornerstone of perioperative care. Nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated superiority in the treatment of biliary colic compared with opioids and antispasmodics, offering additional benefits in reducing the risk of disease progression and need for rescue analgesia [8]. Corticosteroids, through their potent anti-inflammatory properties, have also shown promise in reducing postoperative pain intensity and inflammatory mediator release [9]. Recent evidence suggests that the combination of NSAIDs and corticosteroids may provide synergistic analgesic and anti-inflammatory effects, surpassing the efficacy of either agent alone [10].
This study aims to evaluate the effectiveness of combining NSAIDs with corticosteroids for postoperative pain control in patients undergoing open cholecystectomy. The primary objective is to assess the impact on pain intensity, while the secondary objective is to determine their influence on postoperative complications and recovery profile.

METHODS

This study was designed as a double-blind randomized clinical trial to compare the analgesic and anti-inflammatory effects of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and their combination in patients undergoing elective open cholecystectomy. The trial was conducted in the elective operating theater of RSUD Prof. Dr. Margono Soekarjo, Purwokerto, Indonesia, between May and June 2025. Ethical clearance was obtained from the Institutional Review Board of RSUD Prof. Dr. Margono Soekarjo (approval number: [insert number], issued on [insert date]). Written informed consent was obtained from all participants before enrollment. Eligible participants were adult patients (aged 18–70 years) with American Society of Anesthesiologists (ASA) physical status I–II and body mass index (BMI) between 18–40 kg/m² who underwent elective open cholecystectomy. Exclusion criteria included use of NSAIDs or corticosteroids within 24 hours prior to surgery, allergy to study drugs, uncontrolled diabetes, daily opioid or glucocorticoid use, significant hepatic, renal, cardiac impairment, cognitive or neurologic disorders, history of alcohol or drug abuse, and contraindications to ibuprofen or paracetamol. Patients were excluded if surgery lasted longer than two hours, or if perioperative complications occurred.

Sample size was calculated using a non-inferiority RCT formula with $\alpha = 0.05$ and $\beta = 0.80$, yielding 14 participants per group; anticipating a 10% dropout rate, 15 patients per group were enrolled, for a total of 45 participants. Randomization was performed by simple drawing of lots into three equal groups (1:1:1). Allocation concealment was maintained by sealed opaque envelopes, and the assigned treatment was administered by an anesthesiology resident not involved in outcome assessment. Both patients and investigators were blinded to group allocation.

Patients were randomized into three groups: Group A received paracetamol 1 g IV plus dexamethasone 10 mg IV; Group B received paracetamol 1 g IV plus ibuprofen 400 mg IV; and Group C received paracetamol 1 g IV, dexamethasone 10 mg IV, and ibuprofen 400 mg IV. Paracetamol was administered one hour before the skin incision, while ibuprofen and dexamethasone were administered immediately after the incision. Ibuprofen and dexamethasone were repeated every eight hours, and paracetamol every six hours. All patients received standardized general anesthesia with fentanyl 2 mcg/kg, thiopental 4 mg/kg, and rocuronium 0.6 mg/kg, followed by sevoflurane maintenance (1 MAC, O_2:N_2O 60:40). Prior to skin closure, 0.25% levobupivacaine was infiltrated subcutaneously. Ondansetron 4 mg IV was administered pre-induction for postoperative nausea and vomiting prophylaxis. Rescue analgesia with fentanyl 1 mcg/kg was administered if Numeric Rating Scale (NRS) > 4.

Blood samples were collected one hour before surgery and six hours after the first administration of analgesics. Samples (2 mL) were drawn from the cubital vein, centrifuged at 1000 rpm for 15 minutes, and stored at –20°C until analysis. Plasma prostaglandin E_2 (PGE_2) and interleukin-6 (IL-6) levels were measured using ELISA kits (Elabscience, USA). Pain intensity was assessed with the NRS (0–10) by a trained anesthesiology resident not involved in randomization or drug administration.

All data were entered into REDCap® (Research Electronic Data Capture) and stored securely for one year. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality using Shapiro–Wilk and homogeneity with Levene's test. Normally distributed paired data were analyzed with paired t-tests, while non-normally distributed data were analyzed with Wilcoxon tests. Between-group comparisons were performed using ANOVA with Tukey post hoc testing or Kruskal–Wallis with Dunn's post hoc as appropriate. Categorical variables were analyzed with chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 45 patients were enrolled and randomized equally into three groups:

Group A: Paracetamol + Dexamethasone (n = 15)

Group B: Paracetamol + Ibuprofen (n = 15)

Group C: Paracetamol + Ibuprofen + Dexamethasone (n = 15).

Baseline characteristics including age, gender distribution, BMI, education level, ASA physical status, operative time, intraoperative bleeding, and leukocyte counts were comparable across the three groups, with no statistically significant differences (all p > 0.05). This indicates that the study groups were homogeneous at baseline (Table 1).

Table 1. Demographic and Baseline Characteristics of Patients

Characteristics	Intervention			*p-value*
	Group A (n = 15)	Group B (n = 15)	Group C (n = 15)	
Sex, n (%) - Male - Female	 6 (40,0) 9 (60,0)	 9 (60,0) 6 (40,0)	 7 (46,7) 8 (53,3)	0,537*
Usia, tahun (median, min-maks)	49 (32-65)	53 (35-58)	52 (38-60)	0,650†
Education, n (%) - Elementary School	 1 (6,7)	 6 (40,0)	 5 (33,3)	0,533^

- Junior High School - Senior High School - Diploma - Bachelor	4 (26,7) 7 (46,7) 1 (6,7) 2 (13,3)	3 (20,0) 3 (20,0) 1 (6,7) 1 (6,7)	2 (13,3) 6 (40,0) 1 (6,7) 1 (6,7)	
BMI, n (%) - Normal weight - Overweight	 14 (93,3) 1 (6,7)	 9 (60,0) 6 (40,0)	 10 (66,7) 5 (33,3)	 0,102^
Leukocytes, n (%) - Elevated - Normal	 1 (6,7) 14 (93,3)	 5 (33,3) 10 (46,7)	 2 (13,3) 13 (86,7)	 0,229^
Duration of surgery, minute (mean±SD)	60,0 ± 9,82	61,7 ± 10,5	62,1 ± 10,1	0,123‡
Blood loss, cc (Median, min-max)	180 (100-320)	200 (150-400)	200 (150-500)	0,062†
ASA (Median, min-max)	2 (1-2)	2 (1-2)	2 (1-3)	0,652†

Inflammatory Markers (IL-6 and PGE2)

The distributions of IL-6 and PGE2 levels were non-normal (Shapiro–Wilk $p < 0.001$), hence presented as medians (min–max).

For IL-6, Group C demonstrated a reduction in Δsqrt IL-6 (median −0.56, range −7.93 to 0.81), while Groups A and B showed increases (0.56 and 0.39, respectively). Overall comparison revealed significant differences among groups (Kruskal–Wallis $p = 0.007$). Post hoc Dunn's test showed Group C differed significantly from both Group A ($p = 0.012$) and Group B ($p = 0.004$), whereas Group A vs Group B was not significant ($p = 0.713$).

Table 2. Changes in Serum IL-6 Levels Pre- and Post-Intervention

Δ Sqrt IL-6	**Groups**			***p-value***
	A	**B**	**C**	
Median (min-max)	0,56 (-0,84 to 2,51)	0,39 (-1,22 to 2,70)	-0,56 (-7,93 to 0,81)	
Shapiro wilk test*	0,786	0,953	0,003	
Kruskal wallis				0,007

Group A: Paracetamol + dexamethasone; B: Paracetamol + ibuprofen; C: Paracetamol + ibuprofen + dexamethasone. Negative values indicate decreased IL-6 levels. *: presented in p-value

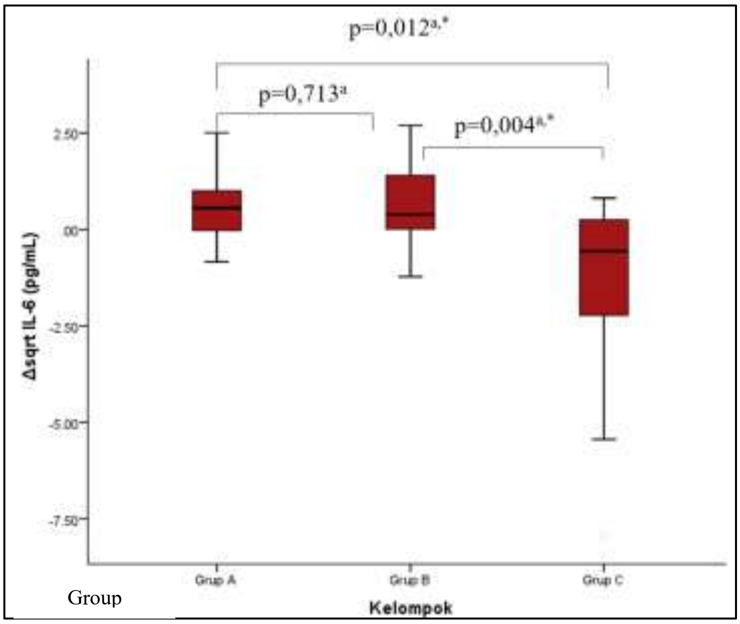

Figure 1. Median Δsqrt IL-6 across Groups

Group A: Paracetamol + dexamethasone, B: Paracetamol + ibuprofen, C: Paracetamol + ibuprofen + dexamethasone. 1: pre-treatment, 2: post-treatment. a: post hoc dunn test

Within-group analysis showed a significant IL-6 decrease in Group C (Wilcoxon $p = 0.047$), a significant increase in Group B ($p = 0.027$), and no significant change in Group A ($p = 0.053$).

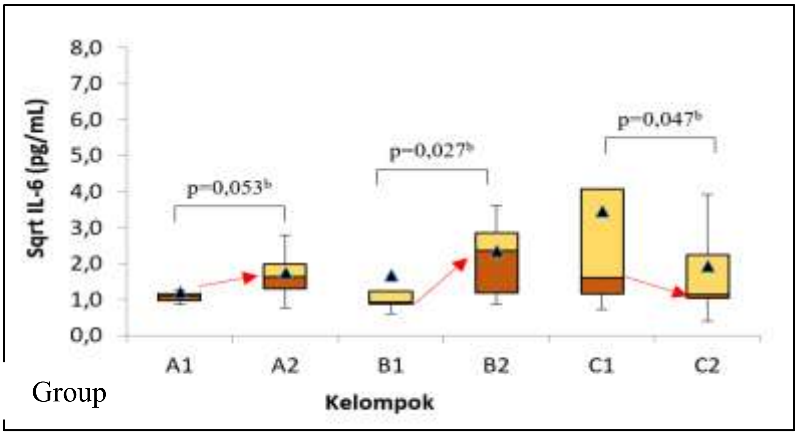

Figure 2. Pre- and Post-Intervention IL-6 Levels within Groups

A: Paracetamol + Dexamethasone; B: Paracetamol + Ibuprofen; C: Paracetamol + Ibuprofen + Dexamethasone. 1: pre-treatment, 2: post-treatment; b. wilcoxon test

For PGE2, Δlog PGE2 did not differ significantly between groups (Kruskal–Wallis $p = 0.276$). Although Group A showed the highest median increase (0.08), intergroup differences were not statistically significant (Table 3, Figure 3). Paired analysis within groups revealed no significant changes from pre- to post-treatment (all $p > 0.05$) (Figure 4).

Table 3. Changes in Serum PGE2 Levels Pre- and Post-Intervention

ΔLog PGE2	**Groups**			***p-value***
	A	**B**	**C**	
Median (min-max)	0,08 (-0,33 to 0,84)	0,03 (-0,17 s.d 0,13)	0,05 (-0,40 to 0,57)	
Shapiro wilk test*	0,010	0,373	0,119	
Kruskal wallis				0,276

Group A: Paracetamol + dexamethasone, B: Paracetamol + ibuprofen, C: Paracetamol + ibuprofen + dexamethasone. *: presented in p-value

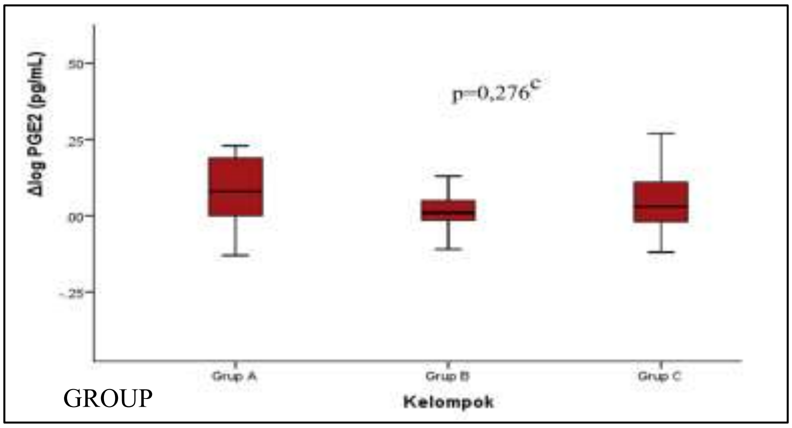

Figure 3. Median Δlog PGE2 across Groups

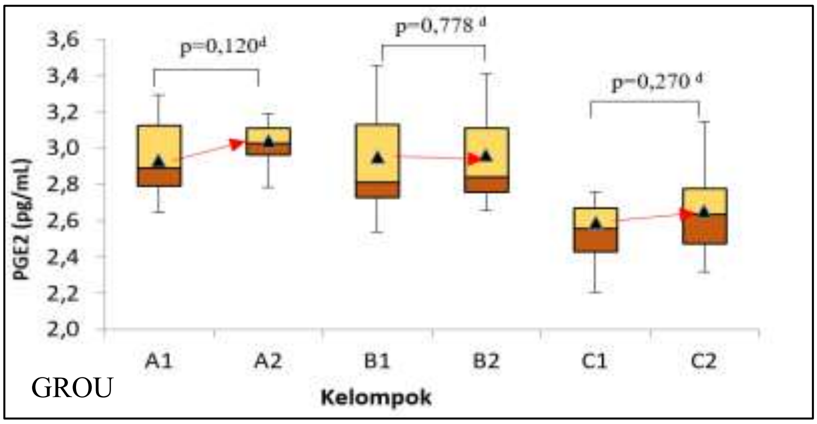

Figure 4. Pre- and Post-Intervention PGE2 Levels within Groups

Analgesic Outcomes (NRS Scores)

Postoperative NRS pain scores differed significantly between groups (Kruskal–Wallis $p < 0.001$). Group C had the lowest median NRS score (2, range 1–2), followed by Group B (3, range 2–3) and Group A (4, range 3–5). Post hoc analysis showed significant differences between all pairs: Group A vs Group B ($p = 0.022$), Group A vs Group C ($p < 0.001$), and Group B vs Group C ($p = 0.001$) (Table 4, Figure 5).

Table 4. Comparison of Median NRS Scores among Groups

Intervention	**NRS Median (Min-Max)**	**p-value**
Paracetamol + Dexamethasone (A)	4 (3-5)	<0,001[c]
Paracetamol + Ibuprofen (B)	3 (2-3)	
Paracetamol + Ibuprofen + Dexamethasone (C)	2 (1-2)	

[c]*Kruskal-Wallis Test*

Table 5. Postoperative NRS Pain Scores across Groups

Intervention	**IL-6**	**PGE2**	**Median NRS**
PCT + dexamethasone (A)	NS	NS	4[a]
PCT + ibuprofen (B)	↑S	NS	3[b]
PCT + dexamethasone + ibuprofen (C)	↓S	NS	2[c]

NS: not significant, S: significant at $p < 0.05$; □: increase; □: decrease; superscript letters a, b, c indicate the comparison of median NRS between two intervention groups (different letters denote significant differences).

STATISTICAL ANALYSIS RESULTS

A repeated measures ANOVA was performed to compare postoperative pain intensity (VAS scores) among the three groups across time points (2, 6, 12, and 24 hours). The analysis showed a significant main effect of time ($F = 42.6$, $p < 0.001$), indicating a progressive decline in pain scores over 24 hours. A significant main effect of group was also observed ($F = 5.13$, $p = 0.010$), suggesting differences in analgesic efficacy among treatment regimens. Moreover, the interaction between group and time was significant ($F = 3.89$, $p = 0.018$), showing that the pattern of pain reduction varied between groups.

Post hoc pairwise comparisons with Bonferroni correction revealed that Group C (Paracetamol + Ibuprofen + Dexamethasone) consistently demonstrated lower pain scores compared to Group A (Paracetamol + Dexamethasone) at 6, 12, and 24 hours postoperatively ($p = 0.021$, $p = 0.008$, and $p = 0.004$, respectively). Group C also had significantly lower scores compared to Group B (Paracetamol + Ibuprofen) at 12 and 24 hours ($p = 0.033$ and $p = 0.012$). No significant differences were found between Group A and Group B at any time point (all $p > 0.05$).

These findings indicate that the triple combination of Paracetamol, Ibuprofen, and Dexamethasone provides superior postoperative analgesia and greater suppression of inflammatory response compared to either dual combination regimen.

DISCUSSION

This randomized controlled trial investigated the effects of combining paracetamol, ibuprofen, and dexamethasone on postoperative pain and inflammatory markers in patients undergoing open cholecystectomy. The main findings showed that the combination regimen significantly reduced pain intensity, as reflected by lower NRS scores, and produced the most favorable anti-inflammatory response on IL-6 levels compared to monotherapy groups. These results suggest that a multimodal regimen provides superior analgesic efficacy and inflammation control in this surgical population [11], [12].

The baseline characteristics of the participants, including demographic and perioperative variables, were homogeneous across groups, thus supporting the validity of comparisons. Although intraoperative blood loss approached statistical significance, it remained above the alpha threshold and was unlikely to affect the main outcomes. This finding aligns with previous studies indicating that well-balanced baseline characteristics reduce confounding effects in clinical trials of perioperative analgesia [13].

Regarding inflammatory markers, our study found that combination therapy significantly reduced IL-6 levels, whereas ibuprofen alone was associated with an increase, and dexamethasone alone did not achieve significant reduction. These results confirm the synergistic anti-inflammatory action of NSAIDs and corticosteroids, as reported in prior research where NSAID-steroid combinations effectively suppressed IL-6 and other cytokine pathways [14], [15], [16]. In contrast, no significant within-group changes were observed for PGE_2, although intergroup comparisons demonstrated lower levels in the combination group. This discrepancy may be due to baseline variability and highlights the complex role of PGE_2 in perioperative inflammation [17], [18].

Analgesic efficacy was most pronounced in the combination group, which recorded the lowest NRS scores compared to either ibuprofen or dexamethasone monotherapy. This finding supports earlier reports that multimodal regimens combining paracetamol, NSAIDs, and corticosteroids provide superior analgesia, often comparable to opioid-based therapy but with fewer adverse effects [19], [20], [21]. Such an approach is clinically

relevant, particularly in minimizing opioid requirements and reducing risks of respiratory depression and delayed recovery [22].
The present study is not without limitations. First, the sample size was relatively small and derived from a single center, which may limit generalizability. Second, the follow-up period was short, with inflammatory markers and pain scores measured only at six hours postoperatively, thereby excluding longer-term dynamics of pain and inflammation. Third, although randomization and double blinding minimized bias, the study did not assess potential adverse effects beyond the early postoperative period.
In conclusion, the combination of paracetamol, ibuprofen, and dexamethasone demonstrated superior efficacy in reducing pain intensity and modulating inflammatory response after open cholecystectomy compared with monotherapy regimens. These findings reinforce the value of multimodal analgesia in perioperative care and suggest that incorporating NSAID-steroid combinations into standard postoperative protocols could enhance recovery while reducing opioid reliance. Future studies with larger multicenter cohorts, extended follow-up, and comprehensive safety evaluations are warranted to confirm these results and establish long-term clinical applicability [23], [24], [25].

CONCLUSION

In patients undergoing elective open cholecystectomy, a multimodal regimen combining paracetamol, ibuprofen, and dexamethasone provided the best overall outcomes compared with dual regimens. The triple-combination group demonstrated the lowest postoperative pain scores (NRS) and the most favorable anti-inflammatory response, shown by a significant reduction in IL-6, while changes in PGE2 were not significantly different across groups. These findings support the use of paracetamol + ibuprofen + dexamethasone as an effective strategy to enhance postoperative analgesia and attenuate early inflammatory response after open cholecystectomy. Given the study's single-center design, modest sample size, and short biomarker follow-up window, larger multicenter trials with longer observation and safety evaluation are recommended to confirm generalizability and inform standardized postoperative protocols.

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