# The impact of intravenous ibuprofen-paracetamol vs. ketorolac-paracetamol on coagulation and inflammation: implications for analgesia in hypertensive patients undergoing surgery



## El impacto de ibuprofeno-paracetamol intravenoso vs. ketorolaco-paracetamol en la coagulación y la inflamación: implicaciones para la analgesia en pacientes hipertensos sometidos a cirugía

Muhammad Khaerul Maarif[1*], AM Takdir Musba[2], Madonna D Datu[3], Syafruddin Gaus[4], Nur Surya Wirawan[5], Andi Adil[6]

[1]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; khaerulmaarif19@yahoo.com; https://orcid.org/0009-0000-2079-5291

[2]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; takdir1974@yahoo.com; https://orcid.org/0000-0002-5685-6903

[3]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; Medical Staff of Anesthesiology, Intensive Care, and Pain Management, Hasanuddin University Hospital, Makassar, Makassar, Indonesia; madonnadatu6@gmail.com; https://orcid.org/0000-0002-6257-4021

[4]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; udhingaus@hotmail.com; https://orcid.org/0000-0003-0380-0954

[5]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; Medical Staff of Anesthesiology, Intensive Care, and Pain Management, Hasanuddin University Hospital, Makassar, Makassar, Indonesia; acoanestesi@yahoo.com; https://orcid.org/0009-0005-4832-7250

[6]Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; Department of Anesthesia, Intensive Care and Pain Management, Hasanuddin University, Makassar, Indonesia; adil_zanetti@yahoo.co.id; https://orcid.org/0000-0002-3637-9513

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**Abstract**

Postoperative pain following gynecological surgery continues to pose a significant clinical challenge, as many patients still experience moderate-to-severe pain with standard treatments. The potential for complications like bleeding further underscores the need for optimized analgesic strategies that balance efficacy with safety. This study evaluated two multimodal regimens: intravenous ibuprofen-paracetamol versus ketorolac-paracetamol, comparing their impact on pain intensity, coagulation parameters, and interleukin-6 (IL-6) levels. In a double-blind randomized trial involving 40 patients, both combinations provided equivalent and effective pain control, with no significant difference in pain scores or clotting time observed between the groups. However, a key finding was that the ketorolac-based regimen caused a significant prolongation of bleeding time at 24 and 48 hours post-surgery. Conversely, the ibuprofen-based combination demonstrated a stronger anti-inflammatory effect, resulting in significantly lower levels of the pro-inflammatory cytokine IL-6. Consequently, while both regimens are effective for analgesia, the choice between them should be influenced by the patient's risk profile; ketorolac may pose a greater bleeding risk, whereas ibuprofen may offer superior control of the surgical inflammatory response.

**Keywords:** Hypertensive Patients, Pain Management, Multimodal Analgesic, Coagulation Profile, Interleukin-6, Ibuprofen, Ketorolac, Paracetamol, Gynecological Surgery.

## Resumen

El dolor posoperatorio tras cirugía ginecológica sigue representando un desafío clínico significativo, ya que muchas pacientes aún experimentan dolor de moderado a intenso con los tratamientos estándar. La posibilidad de complicaciones, como el sangrado, subraya aún más la necesidad de estrategias analgésicas optimizadas que equilibren eficacia y seguridad. Este estudio evaluó dos regímenes multimodales: ibuprofeno-paracetamol intravenoso versus ketorolaco-paracetamol, comparando su impacto en la intensidad del dolor, los parámetros de coagulación y los niveles de interleucina-6 (IL-6). En un ensayo aleatorizado doble ciego con 40 pacientes, ambas combinaciones proporcionaron un control del dolor equivalente y efectivo, sin observarse diferencias significativas en las puntuaciones de dolor ni en el tiempo de coagulación entre los grupos. Sin embargo, un hallazgo clave fue que el régimen basado en ketorolaco provocó una prolongación significativa del tiempo de sangrado a las 24 y 48 horas posoperatorias. Por el contrario, la combinación basada en ibuprofeno demostró un efecto antiinflamatorio más potente, resultando en niveles significativamente más bajos de la citocina proinflamatoria IL-6. En consecuencia, si bien ambos regímenes son eficaces para la analgesia, la elección entre ellos debe depender del perfil de riesgo del paciente; el ketorolaco puede suponer un mayor riesgo de sangrado, mientras que el ibuprofeno puede ofrecer un mejor control de la respuesta inflamatoria quirúrgica.



**Palabras clave**: Pacientes hipertensos, Manejo del dolor, Analgésico multimodal, Perfil de coagulación, Interleucina-6, Ibuprofeno, Ketorolaco, Paracetamol, Cirugía ginecológica.


## Introduction

Effective postoperative pain control in gynecologic surgery is crucial, as inadequate management may impair recovery, which frequently results in postoperative pain of varying intensity, ranging from moderate to severe[1]. Inadequate perioperative pain management can lead to several morbidities, including hemodynamic instability, prolonged recovery time, immunosuppression, and an increased risk of developing chronic pain [2]. Postoperative pain following gynecological procedures may arise from various surgical approaches, including laparotomy and laparoscopy[2]. Although laparoscopy is considered a minimally invasive technique, postoperative pain remains a significant concern that warrants appropriate management. Postoperative pain involves a combination of nociceptive, inflammatory, and neuropathic components resulting from tissue injury and the inflammatory response to surgical trauma[3]. Therefore, a multimodal analgesic approach that combines multiple drugs with different mechanisms of action is strongly recommended to achieve optimal pain control while minimizing the adverse effects associated with high doses of a single agent[4].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Paracetamol (Acetaminophen) are central components in multimodal postoperative analgesia. Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor that reduces the production of prostaglandins, which are involved in pain and inflammation. Ketorolac is a more potent NSAID with strong analgesic effects and is frequently administered intravenously for the management of severe postoperative pain[5]. Paracetamol, although its mechanism of action is not fully understood, is believed to act centrally to exert analgesic and antipyretic effects [6]. Despite their effectiveness, NSAIDs are associated with potential side effects, particularly affecting the coagulation and gastrointestinal systems. All NSAIDs can inhibit platelet aggregation to varying degrees, with Ketorolac being associated with a higher risk of bleeding due to its greater potency[7]. Postoperative coagulation disturbances may lead to serious hemorrhagic complications, especially in surgeries with significant bleeding potential, such as gynecological procedures. Moreover, the postoperative inflammatory response—mediated by pro-inflammatory cytokines such as Interleukin-6 (IL-6)—is also of concern. IL-6 is released in response to tissue injury and correlates with pain intensity and the overall postoperative stress response[8-10]. NSAIDs are known to modulate this inflammatory cascade. Comparing the effects of different analgesic combinations on IL-6 levels can provide insights into their capacity to attenuate systemic inflammation.

Given the importance of achieving effective pain control with a favorable safety profile, this study aimed to

compare the efficacy and safety of two commonly used analgesic combinations—Ibuprofen-Paracetamol and Ketorolac-Paracetamol—in patients undergoing gynecological surgery. This comparison focused on postoperative pain intensity, changes in coagulation parameters (CT, BT), and serum Interleukin-6 levels. Furthermore, to our knowledge, no prior studies have compared their effects on interleukin-6 levels, which provides insight into the postoperative inflammatory response.

Given the importance of achieving effective pain control with a favorable safety profile, this study aimed to compare the efficacy and safety of two commonly used analgesic combinations patients undergoing gynecological surgery. This comparison focused on postoperative pain intensity, changes in coagulation parameters (CT, BT), and serum Interleukin-6 levels. Furthermore, to our knowledge, no prior studies have compared their effects on interleukin-6 levels, which provides insight into the postoperative inflammatory response. These considerations are particularly relevant for patients with hypertension, who often present with compromised vascular integrity and altered coagulation profiles. The differential effects of these analgesic regimens on bleeding risk and inflammatory modulation may have significant implications for perioperative management in this vulnerable population, potentially influencing cardiovascular outcomes and recovery trajectories.

## Materials and methods

### Study Design and Ethical Approval

A double-blind, randomized clinical trial was conducted between December 2024 and March 2025 at Dr. Wahidin Sudirohusodo General Hospital and its affiliated network hospitals. The study design was approved by the Research Ethics Committee of Hasanuddin University (No:1010/UN4.6.4.5.31/PP36/2024).

### Participant Selection and Eligibility

Eligible patients were patients aged 18-65 years undergoing gynecologic surgery and had an American Society of Anesthesiologists (ASA) physical status I-II. Patients with relevant comorbidities (e.g., asthma, cardiovascular disease, epilepsy, psychiatric disorders, diabetes, renal or hepatic impairment, hematologic or immunologic disorders), history of alcohol or prior analgesic/anti-inflammatory drug use, chemotherapy, or allergies to study medications were excluded. In addition, patients receiving heparin, experiencing major bleeding or transfusion (>40% MABL), withdrawing from the study, or converted to general anesthesia were also excluded. After obtaining informed consent, the samples were divided into two groups: Group 1 (ibuprofen + paracetamol) and Group 2 (ketorolac + paracetamol).

### Randomization and Blinding Procedure

After informed consent was obtained and the inclusion criteria were met, the patients were randomly assigned to the treatment groups using block randomization with a block size of four, generated by a computer-based random number generator. Group allocations were placed in sealed, opaque envelopes and opened by a nurse who was not involved in the data collection or patient evaluation.

Both the anesthesiologist responsible for postoperative pain management and the researcher collecting data were blinded to the group allocation (double-blind). Patients were also unaware of the medications they received (double-blind).



### Anesthesia and Surgical Protocol

All patients underwent standardized spinal anesthesia in the left lateral decubitus position using a 25-G needle at the L2–L3 interspace, with intrathecal bupivacaine 15 mg plus fentanyl 25 µg. Surgery was initiated after achieving a sensory block to T4 with a Bromage score of 0/0.

### Intervention Protocol

After surgery was completed and the patient had recovered from anesthesia in the Post-Anesthesia Care Unit (PACU), the assigned analgesic regimen was administered 1 hour postoperatively according to group allocation. Group 1 (Ibuprofen-Paracetamol) received Ibuprofen 400 mg diluted in 100 mL of 0.9% NaCl plus 10 mL of placebo every 8 hours and Paracetamol 1000 mg intravenously every 6 hours. Group 2 (Ketorolac-Paracetamol) received Ketorolac 30 mg diluted in 10 mL of 0.9% NaCl plus 100 mL of placebo every 8 hours and Paracetamol 1000 mg intravenously every 6 hours. Medications were administered for the first 24 hours postoperatively. If pain was not adequately controlled with the assigned regimen (NRS > 4), rescue analgesia in the form of intravenous Fentanyl at a dose of 0.5–1 mcg/kg body weight was provided. The total dose of rescue analgesia administered was recorded.

### Outcome Measures and Data Collection

The primary endpoints were pain levels, coagulation profile, and serum interleukin-6 (IL-6) levels. Pain intensity was assessed using the numeric rating scale (NRS) at 6, 12, 24, and 48 hours postoperatively. Coagulation profile parameters, specifically clotting time (CT) and bleeding time (BT), were measured 2 hours before surgery (preoperative baseline) and at 24 and 48 hours postoperatively. IL-6 levels were measured 2 hours before surgery (preoperative baseline) and at 6 and 24 hours post-surgery using the Enzyme-Linked Immunosorbent Assay (ELISA) method. Blood samples were collected, and IL-6 concentration was analyzed to evaluate the inflammatory response to the surgical procedure and analgesic intervention.

### Statistical Analysis

Data were analyzed using the SPSS version 25.0 statistical software. The normality of the data was assessed using the Shapiro-Wilk test, with a significance level of $p > 0.05$ indicating a normal distribution. For normally distributed data ($p > 0.05$), an independent t-test was used, whereas for non-normally distributed data ($p \leq 0.05$), the Mann-Whitney U test and the Wilcoxon test were applied to compare NRS scores, CT, BT, and IL-6 levels before and after the intervention within each group. A P value of <0.05 was considered statistically significant.

This study included a total of 40 participants who were randomly divided into two groups. The baseline characteristics of the two groups (age, body weight, height, BMI, duration of surgery, and blood loss) showed no significant differences (p>0.05), indicating that the groups were homogeneous. Detailed characteristics are presented in Table 1.

**Table 1. Characteristics of research subjects**

| Characteristics | Group P1; (n = 20) | Group P2; (n = 20) | p-value |
|---|---|---|---|
| | Mean ± SD/ Median (min-max) | Mean ± SD/ Median (min-max) | |
| Age (year) | 40,30 ± 7,39 | 41,50 ± 10,29 | 0,674[a] |
| Body weight (kg) | 64,10 ± 8,54 | 61,55 ± 5,67 | 0,273[a] |
| Height (m) | 155,00 (145,00-165,00) | 156,00 (150,00-161,00) | 0,183[b] |
| Body Mass Index (kg/m$^2$) | 26,86 (20,88-40,00) | 24,45 (21,64-32,00) | 0,157[b] |
| Operation duration (minutes) | 120,00 (90,00-180,00) | 120,00 (60,00-180,00) | 0,102[b] |
| Bleeding (mL) | 300,00 (150,00-500,00) | 300,00 (150,00-500,00) | 0,925[b] |

An independent sample t-test, Mann-Whitney test; *p-value* <0.05 is significant.

### Pain Levels

Pain levels were assessed using the Numeric Rating Scale (NRS) at rest and during movement at 6, 12, 24, and 48 hours postoperatively. No significant differences were observed in the mean NRS scores at rest or during movement between Group 1 and Group 2 at any of the measurement time points ($p > 0.05$). The comparative results are presented in Table 2 and illustrated in Tables 2 and 3.

**Table 2. Comparison of NRS at rest and NRS during movement between groups**

| | Group P1; (n = 20) | Group P2; (n = 20) | p-value |
|---|---|---|---|
| | Median (min-max) | Median (min-max) | |
| NRS at rest | | | |
| 6 hours post-surgery | 4,00 (3,00-4,00) | 4,00 (3,00-4,00) | 0,183 |
| 12 hours post-surgery | 3,00 (2,00-4,00) | 3,00 (2,00-4,00) | 0,134 |
| 24 hours post-surgery | 2,00 (2,00-3,00) | 2,00 (2,00-3,00) | 0,091 |
| 48 hours post surgery | 1,00 (1,00-2,00) | 1,00 (1,00-1,00) | 0,602 |
| NRS upon movement | | | |
| 6 hours post-surgery | 3,00 (2,00-3,00) | 3,00 (2,00-4,00) | 0,752 |
| 12 hours post-surgery | 2,00 (1,00-2,00) | 2,00 (1,00-4,00) | 0,349 |
| 24 hours post-surgery | 1,00 (1,00-2,00) | 2,00 (1,00-3,00) | 0,524 |
| 48 hours post surgery | 0,00 (0,00-0,00) | 0,00 (0,00-1,00) | 0,152 |

Mann-Whitney test, *p-value* <0.05 is significant.

### Coagulation Profile

As shown in Table 3, there were no significant differences in clotting time (CT) values within either Group 1 or Group 2 across the measurement time points ($p > 0.05$). For bleeding time (BT), Group 1 also did not exhibit significant changes. However, in Group 2, significant differences in BT values were observed between 2 hours preoperatively and 24 hours postoperatively, between 2 hours preoperatively and 48 hours, and between 24 and 48 hours postoperatively ($p < 0.05$).

**Table 3. Comparison of CT and BT between study times**

| Time | Group P1; (n = 20) | p-value | Group P2; (n = 20) | p-value |
|---|---|---|---|---|
| | Mean ± SD/ Median (min-max) | | Mean ± SD/ Median (min-max) | |
| CT (minutes)[a] | | | | |
| 2 hours preoperative | 7,67 ± 0,36 | 1,000 | 7,62 ± 0,36 | 0,772 |
| 24 hours post-surgery | 7,67 ± 0,36 | | 7,67 ± 0,38 | |
| 2 hours preoperative | 7,67 ± 0,36 | 0,104 | 7,62 ± 0,36 | 0,209 |
| 48 hours post surgery | 7,72 ± 0,34 | | 7,76 ± 0,36 | |
| 24 hours post-surgery | 7,67 ± 0,36 | 0,104 | 7,67 ± 0,38 | 0,056 |
| 48 hours post surgery | 7,72 ± 0,34 | | 7,76 ± 0,36 | |
| BT (minutes)[b] | | | | |
| 2 hours preoperative | 3.50 (3.00-3.75) | 0,317 | 3.25 (3.00-3.75) | 0,046 |
| 24 hours post-surgery | 3.50 (3.00-4.00) | | 3.50 (3.00-3.75) | |
| 2 hours preoperative | 3.50 (3.00-3.75) | 0,074 | 3.25 (3.00-3.75) | 0,002 |
| 48 hours post surgery | 3.50 (3.00-3.75) | | 3.75 (3.00-4.00) | |
| 24 hours post-surgery | 3.50 (3.00-4.00) | 0,336 | 3.50 (3.00-3.75) | 0,044 |
| 48 hours post surgery | 3.50 (3.00-3.75) | | 3.75 (3.00-4.00) | |

[a]Paired t test, [b]Wilcoxon test, *p* value <0.05 is significant.

As presented in Table 4, the comparison of changes (Δ) in clotting time (CT) showed no significant differences

between the two groups at 2 hours preoperatively to 24 hours postoperatively (p = 0.429), 2 hours preoperatively to 48 hours postoperatively (p = 0.265), and 24 to 48 hours postoperatively (p = 0.583). Regarding changes in bleeding time (BT), there was also no significant difference between the groups at 2 hours preoperatively to 24 hours postoperatively (p = 0.201) and 24 to 48 hours postoperatively (p = 0.157). However, at 2 hours preoperatively to 48 hours postoperatively, Group P2 demonstrated a significantly greater increase in BT compared to Group P1 (p = 0.021).

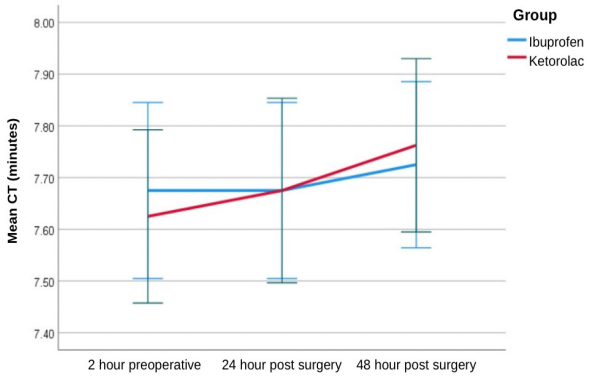
**Table 4. Comparison of CT and BT changes between groups**

| Time | Group P1; (n = 20) Median (min-max) | Group P2; (n = 20) Median (min-max) | p-value |
|---|---|---|---|
| Delta CT (minutes) | | | |
| 2 hours pre-24 hours post | 0.00 (0.00-0.00) | 0.00 (0.00-0.50) | 0,429 |
| 2 hours pre-48 hours post | 0.00 (0.00-0.50) | 0.00 (0.00-0.75) | 0,265 |
| 24 hours post-48 hours post | 0.00 (0.00-0.50) | 0.00 (0.00-0.50) | 0,583 |
| Delta BT (minutes) | | | |
| 2 hours pre-24 hours post | 0.00 (0.00-0.50) | 0.13 (-0.25-0.50) | 0,201 |
| 2 hours pre-48 hours post | 0.00 (-0.17-0.50) | 0.25 (0.00-0.50) | 0,021 |
| 24 hours post-48 hours post | 0.00 (-0.25-0.50) | 0.25 (-0.25-0.55) | 0,157 |

Mann-Whitney test, *p-value* <0.05 is significant.

The trends in CT and BT for both groups are illustrated in Figures 1 and 2. CT remained relatively stable in the Ibuprofen group, whereas a slight increase was observed in the Ketorolac group. BT showed minimal changes in the Ibuprofen group but increased more notably in the Ketorolac group, particularly at 48 hours postoperatively.

**Figure 1. CT graph in both groups**




## Interleukin-6 Levels

The results presented in Table 5 indicate no significant difference in the mean IL-6 levels at 2 hours preoperatively between Group 1 and Group 2 (p > 0.05), indicating comparable baseline IL-6 levels in both groups. However, IL-6 levels differed significantly between the two groups at 6 hours and 24 hours postoperatively (p < 0.05). The comparison of IL-6 levels between the groups over the study time points is illustrated in Figure 5. IL-6 levels increased from 2 hours preoperatively to 6 hours postoperatively, followed by a decline at 24 hours postoperatively in both groups.

**Figure 2. The BT graph in both groups**

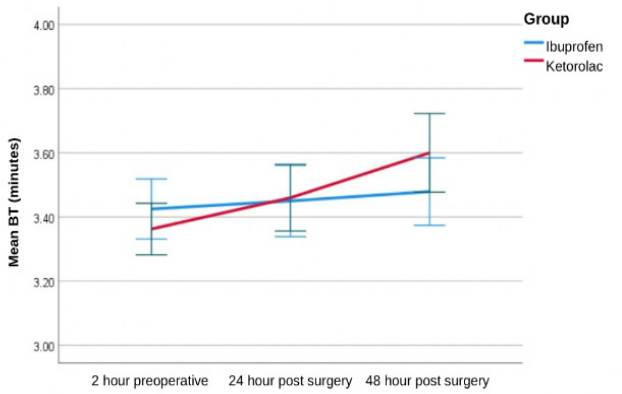
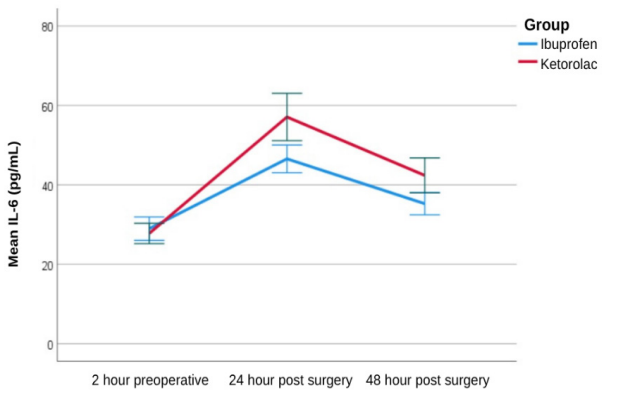



**Table 5. Comparison of IL-6 levels between groups**

| Time | IL-6 (pg/mL) | | p-value |
|---|---|---|---|
| | Group P1; (n = 20) | Group P2;(n = 20) | |
| | Median (min-max) | Median (min-max) | |
| 2 hours preoperative | 29,00 (14,87-39,00) | 27,84 (18,97-35,04) | 0,522 |
| 6 hours post-surgery | 43,81 (35,30-59,83) | 52,58 (40,00-81,00) | 0,003 |
| 24 hours post-surgery | 34,50 (22,00-49,92) | 43,00 (23,00-61,13) | 0,007 |

Mann-Whitney test, *p-value* <0.05 is significant.

**Table 3. IL-6 levels in both groups**



This study compared the analgesic efficacy, effects on coagulation profiles, and inflammatory responses of the Ibuprofen-Paracetamol combination versus the Ketorolac-Paracetamol combination in patients undergoing gynecological surgery. The findings demonstrated that both analgesic combinations—paracetamol-ibuprofen and paracetamol-ketorolac—were effective in managing postoperative gynecological pain, with no significant differences observed in Numeric Rating Scale (NRS) scores. These results are consistent with prior research by [11], which similarly reported no significant differences in pain levels between the paracetamol-ibuprofen and paracetamol-ketorolac combinations following gynecological surgery [10,11]. This supports the principle of multimodal analgesia, wherein drug combinations may produce synergistic effects in reducing pain and opioid consumption.

The absence of a significant difference in NRS pain scores between the two groups indicates that both Ibuprofen-Paracetamol and Ketorolac-Paracetamol combinations provide comparable analgesia in this patient population. This finding supports the concept of multimodal analgesia, where combining drugs with different mechanisms can provide effective pain relief—even though intravenous ketorolac is typically viewed as more potent than oral ibuprofen. The efficacy of paracetamol as a foundational component in both regimens likely contributed to these outcomes, given its well-established analgesic properties in postoperative pain management[2].

An important aspect of this study was the evaluation of coagulation profiles. Although both combinations provided equivalent analgesia, significant differences were observed in the coagulation profiles and IL-6 levels. The ketorolac-paracetamol group exhibited a significant prolongation of bleeding time (BT) at 24 and 48 hours postoperatively. Ketorolac is known to cause prolonged bleeding time and reduced platelet aggregation [12,13]. In contrast, paracetamol exerts minimal effects on platelet aggregation and does not significantly prolong the bleeding time [14]. Although classified as an NSAID, Ibuprofen has been reported to have effects on platelet aggregation and coagulation that return to normal within 24 hours after the last dose [15,16]. The increased bleeding time observed in the ketorolac-paracetamol group indicates a potentially higher risk of bleeding compared to the ibuprofen-paracetamol group, particularly in surgical procedures requiring meticulous hemostatic control.

Furthermore, this study also examined the effects on serum IL-6 levels, an important inflammatory marker. The ibuprofen-paracetamol group demonstrated a more significant reduction in serum IL-6 levels at 6 and 24 hours postoperatively compared to the ketorolac-paracetamol group. IL-6 is a pro-inflammatory cytokine released in response to tissue injury and surgical stress [17], and it correlates with systemic inflammatory response and pain intensity [18,19]. The greater suppression of IL-6 by the ibuprofen-paracetamol combination may reflect the stronger anti-inflammatory effects of ibuprofen compared to ketorolac. This suggests that ibuprofen may be more effective in modulating the systemic inflammatory response following surgery. Such a mechanism could contribute to improved patient recovery, although further investigations are warranted.

The strengths of this study include a double-blind randomized clinical trial design, which helps minimize bias. Objective measurements, such as coagulation parameters and IL-6 levels, further enhanced data robustness. However, several limitations of this study should be noted. This study is limited by its relatively small sample size and short follow-up period of 48 hours, which may restrict the assessment of long-term outcomes and adverse effects. Additionally, the single-center design may limit the generalizability of the results. Therefore, further studies with extended follow-up are necessary to comprehensively evaluate the safety profiles of these analgesic regimens.

The findings of this study support that the combination of Ibuprofen-Paracetamol offers analgesic efficacy equivalent to that of Ketorolac-Paracetamol in gynecological patients, with a more favorable coagulation profile. This suggests that Ibuprofen-Paracetamol may represent a safer analgesic option, particularly for patients at risk of bleeding or those undergoing procedures with a high potential for hemorrhage. In addition, it also has a better anti-inflammatory effect.

Future research should include longer follow-up durations to evaluate the long-term impact on morbidity related to bleeding and chronic pain. Broader investigations of inflammatory markers and more comprehensive assessments of platelet function would also provide deeper insights into the mechanisms of action of these drug combinations. In addition, studies assessing the cost-effectiveness and patient satisfaction of both regimens are highly valuable.

## Conclusions

The combinations of Ibuprofen-Paracetamol and Ketorolac-Paracetamol demonstrated comparable efficacy in managing postoperative pain in gynecological patients. Ibuprofen-Paracetamol combination did not significantly affect coagulation profiles (CT and BT), whereas the Ketorolac-Paracetamol combination significantly influenced coagulation profiles, specifically bleeding time (BT), at 24- and 48-hours post-surgery. Ibuprofen-Paracetamol combination resulted in lower IL-6 levels at 6 and 24 hours postoperatively compared to the Ketorolac-Paracetamol combination, showing that more effective in suppressing the inflammatory response. The selection of an analgesic regimen should carefully balance pain control efficacy, coagulation safety profile, and the need to modulate the inflammatory response on an individual patient basis.

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