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ORIGINAL ARTICLE

Comparison of IL-6 Levels After Ibuprofen–Paracetamol–Dexamethasone in Percutaneous Nephrolithotomy Patients: an Analytic Observational Study

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Abstract

Introduction: Percutaneous Nephrolithotomy (PCNL) is the therapeutic procedure of choice for kidney stones. IL-6 secretion is stimulated during a secondary inflammatory response due to tissue injury or infection. Proper administration of analgesics can reduce morbidity rates, reduce treatment days, and reduce financing.

Patients and Methods: An analytical observational study with a cross-sectional design at Purwokerto tertiary hospital in the period from December 2024 to January 2025 in patients undergoing PCNL procedures and receiving ibuprofen, paracetamol, and dexamethasone therapy, which met the inclusion and exclusion criteria. The observational group (15 patients each) was: Group A 1000 mg paracetamol and 400 mg ibuprofen and 5 mg dexamethasone; Group B 1000 mg paracetamol and 400 mg ibuprofen. IL-6 levels were measured before and 2 hours after the PCNL procedure. IL-6 levels were measured by ELISA (enzyme-linked immunosorbent assay). Comparative analysis of pre- or post-PCNL IL-6 levels by type of analgesic using unpaired t-test, while the comparison of changes in IL-6 levels was analyzed with the Mann-Whitney test. To determine whether the data distribution was normal, we used the Shapiro-Wilk test. The analysis used SPSS version 25.

Results: Pre- and post-PCNL IL-6 levels were significantly lower in Group A compared to Group B ($p < 0.05$). However, changes in IL-6 levels were not statistically significant ($p = 0.787$). Effect size analysis indicated only a small and clinically negligible difference.

Conclusion: There was no significant difference in IL-6 levels post-PCNL between the two observation groups.

Keywords: Dexamethasone, Ibuprofen, IL6, Paracetamol, PCNL

Perbandingan Kadar IL-6 Setelah Pemberian Ibuprofen–Paracetamol–Deksametason pada Pasien Percutaneous Nephrolithotomy: Studi Observasional Analitik

Abstrak

Pendahuluan: *Percutaneous Nephrolithotomy* (PCNL) adalah prosedur terapi pilihan untuk batu ginjal. Sekresi IL-6 distimulasi selama respon inflamasi sekunder akibat cedera jaringan atau infeksi. Pemberian analgetik yang tepat dapat menurunkan angka morbiditas, menurunkan hari perawatan dan menurunkan pembiayaan.

Pasien dan Metode: Penelitian observasional analitik dengan desain cross sectional di rumah sakit tersier Purwokerto pada periode Desember 2024 hingga Januari 2025 pada pasien yang menjalani prosedur PCNL dan mendapat terapi ibuprofen, paracetamol dan dexametason, yang memenuhi kriteria inklusi dan eksklusi. Kelompok observasional (masing-masing 15 pasien) adalah: Kelompok A 1000 mg parasetamol dan 400 mg ibuprofen dan 5 mg deksametason; Kelompok B 1000 mg parasetamol dan 400 mg ibuprofen. Kadar IL6 diukur sebelum dan 2 jam setelah prosedur PCNL. Kadar IL6 diukur dengan ELISA (*Enzyme-linked immunosorbent assay*). Analisis perbandingan kadar IL-6 pre ataupun post PCNL menurut jenis analgesik menggunakan uji t tidak berpasangan, sedangkan perbandingan perubahan kadar IL-6 dianalisis dengan uji *Mann Whitney*. Analisis normalitas sebaran data dilakukan menggunakan uji *Shapiro Wilk*. Analisis menggunakan SPSS versi 25.

Hasil: Kadar IL-6 pre dan post-PCNL lebih rendah secara signifikan pada kelompok A dibandingkan kelompok B ($p < 0,05$). Namun, perubahan kadar IL-6 antara kedua kelompok tidak berbeda signifikan ($p = 0,787$). Analisis effect size menunjukkan efek kecil dengan interval kepercayaan yang lebar, sehingga perbedaan antar kelompok dianggap terbatas dan tidak bermakna secara klinis.

Kesimpulan: Tidak ada perbedaan yang signifikan dalam kadar IL-6 pasca PCNL antara dua kelompok observasi.

Kata kunci: Dexametasone, Ibuprofen, IL6, Paracetamol, PCNL

Introduction

Nephrolithiasis is a common condition marked by the formation of stones within the renal collecting system. Its prevalence is steadily rising worldwide, with the WHO estimating that 12% of the global population will experience nephrolithiasis at least once in their lifetime.[1] For cases involving large kidney stones or those resistant to conservative treatment, percutaneous nephrolithotomy (PCNL) has become the primary therapeutic approach. Although considered a minimally invasive procedure, PCNL can still provoke inflammatory responses due to tissue trauma during the procedure.[2]

Postoperative inflammatory responses can be monitored via biomarkers such as interleukin-6 (IL-6), a proinflammatory cytokine secreted by various cell types in response to tissue injury. Elevated IL-6 levels have been associated with pain severity and the likelihood of postoperative complications. Therefore, multimodal analgesia is crucial. A combination of drugs such as ibuprofen (NSAID), paracetamol (antipyretic), and dexamethasone (corticosteroid) — each with distinct anti-inflammatory mechanisms — can offer optimal suppression of the inflammatory response.[3,4]

However, data on the effectiveness of this drug combination in reducing IL-6 levels in PCNL patients remain limited in Indonesia.[5] This study aims to address this gap by evaluating whether adding dexamethasone to an ibuprofen-paracetamol regimen offers additional benefits in reducing systemic inflammation, as represented by post-procedural IL-6 levels.

Patients and Methods

This was an analytical cross-sectional observational study conducted at Purwokerto tertiary hospital, between December 2024 and January 2025. Informed consent and ethical clearance were obtained from the research ethics committee (Ref number: 010/KEPK/PE/I/2025). Subjects were adult patients aged 18–65 years undergoing PCNL who met the inclusion criteria and provided informed consent. Patients were excluded if they had received anti-inflammatory medication within 48 hours before the procedure or had autoimmune or active infectious diseases.

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To minimize selection bias, strict inclusion and exclusion criteria were applied, and purposive consecutive sampling was used. Baseline characteristics such as age, gender, BMI, leukocyte count, ASA score, and procedure duration were compared between groups to ensure homogeneity. Potential confounders were controlled statistically. Variables with $p < 0.25$ in univariate analysis were included in a multivariate linear regression model to adjust for their effects on IL-6 levels, allowing assessment of the independent association between analgesic regimen and IL-6 outcomes.

Sample size was calculated for two independent means, assuming a 2.0 pg/mL difference in IL-6 levels between groups, a standard deviation of 2.5, 80% power, and 5% significance. This yielded a requirement of 15 subjects per group, resulting in a total of 30 patients.

Participants were allocated into two groups. Group A received 400 mg ibuprofen, 1000 mg paracetamol, and 5 mg dexamethasone intravenously 30 minutes before the procedure.

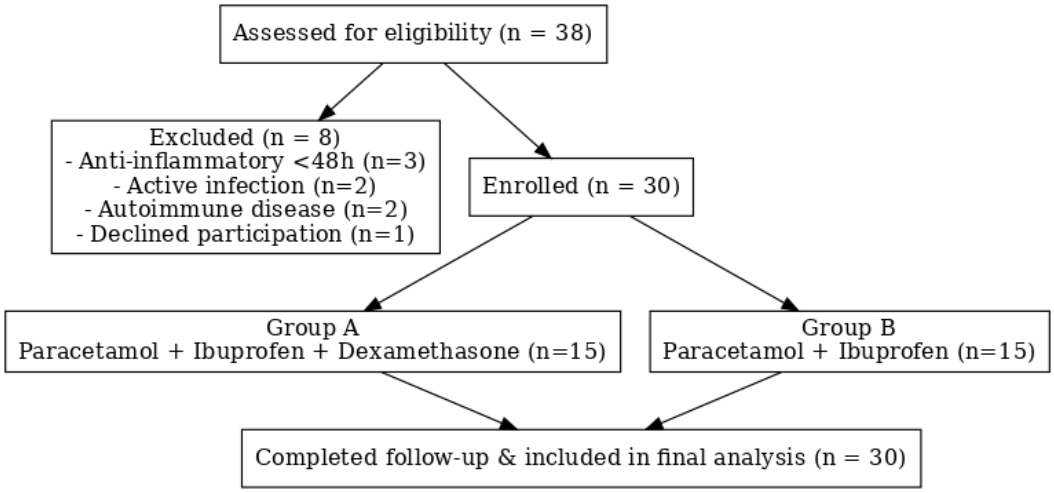

Figure 1. Flow chart of patient recruitment and exclusion process.*

**Thirty patients were enrolled and equally divided between the two groups. The mean age in Group A was 45.6 ± 8.2 years, and in Group B, 44.9 ± 7.5 years. No significant differences were observed in gender distribution or procedure duration between groups.*

Group B received 400 mg ibuprofen and 1000 mg paracetamol. Each group consisted of 15 patients. Blood samples were collected twice—from each patient before and two hours after PCNL—to measure IL-6 levels using enzyme-linked immunosorbent assay (ELISA).

Data were analyzed using SPSS version 25. Normality was assessed with the Shapiro–Wilk test. For normally distributed data, the independent t-test was applied; for non-normally distributed data, the Mann–Whitney test was used. A p-value < 0.05 was considered statistically significant.

Results

A total of 38 patients scheduled for PCNL during the study period were screened for eligibility. Eight were excluded: three had received anti-inflammatory drugs within 48 hours prior to the procedure, two had active infection, two had autoimmune disease, and one declined participation. The remaining 30 patients were enrolled, allocated equally into two groups (n = 15 each), and all completed the study.

Table 1. Patient Characteristics Between Groups

Characteristics	Analgesic types		*p*
	Group A (n = 15)	Group B (n = 15)	
Age, median (min-max) years	52 (38-60)	53 (35-58)	0.884*
Gender, n (%)			
- Male	7 (46.7)	9 (60.0)	0.464^
- Female	8 (53.3)	6 (40.0)	
Education, n (%)			
- SD	5 (38.1)	6 (40.0)	0.833#
- SMP	2 (13.3)	3 (20.0)	
- SMA	6 (40,0)	3 (20,0)	
- D3	1 (6.7)	1 (6.7)	
- S1	1 (6.7)	2 (13.3)	

BMI, n (%)			
- Normal	10 (66.7)	9 (60.0)	0.705^
- Overweight	5 (33.3)	6 (40.0)	
Leukocyte levels, n (%)			
- Above normal	13 (86.7)	10 (66.7)	0.390#
- Normal	2 (13.3)	5 (33.3)	
Surgery duration, median (min-max) minutes	60 (50-80)	60 (50-80)	0.911*
Bleeding volume, median (min-max) cc	200 (150-400)	200 (150-500)	0.743*
ASA score, median (min-max)	2 (1-3)	2 (1-2)	0.608*

*A: paracetamol, ibuprofen & dexamethasone, B: paracetamol & ibuprofen, ^: fisher exact, *: t independen, †: Mann whitney*

Table 1 shows that there were no significant differences in patient characteristics based on the type of analgesic used, as the proportions of each characteristic between Group A and B were not significantly different ($p > 0.05$). It can thus be concluded that patient characteristics were homogeneous and did not confound the effect of analgesic type on IL-6 levels. The median age in Group A was 52 years, similar to that of Group B ($p = 0.884$, Mann-Whitney test). In terms of sex, Group A had a higher proportion of female patients (53.3%), whereas Group B had more male patients (60.0%), though this difference was not statistically significant ($p = 0.464$, Chi-square test). The proportion of patients with elementary school education was similar between Group A and B (38.1% and 40.0%, respectively). Junior high school education was more prevalent in Group B (20.0%) than in Group A (13.3%), while high school education was more common in Group A (40.0%) than in Group B (20.0%). Both groups had equal proportions of diploma (D3) holders, and Group B had a slightly higher proportion of bachelor's degree (S1) holders. Fisher's exact test yielded a p-value of 0.833, indicating comparable educational backgrounds. Regarding BMI, the majority in both Group A and B were of normal weight (66.7% and 60.0%, respectively; $p = 0.705$). Most patients in both groups also had elevated leukocyte levels (86.7% and 66.7%; $p = 0.390$). The mean duration of surgery was identical in both groups at 60 minutes (range 50–80 minutes; $p = 0.911$). The median volume of bleeding was also identical at 200 cc, with a range of 150–400 cc in Group A and 150–500 cc in Group B ($p = 0.743$). The median ASA score was 2 in both groups (range 1–3 in Group A and 1–2 in Group B; $p = 0.608$). No significant differences were observed in operative time, blood loss, or ASA scores ($p > 0.05$ for each, Mann-Whitney test).

Table 2. Comparison of Pre- and Post-PCNL IL-6 Levels Between Analgesic Groups

Measurement time	IL-6 levels (pg/ml)		p-value
	Group A (n = 15)	Group B (n = 15)	
Pre PCNL	0.75 (0.13 – 7.68) (95% CI: 0.3–1.2)	4.00 (0.31 – 96.4) (95% CI: 2.1–5.9)	0.001
Post PCNL	1.25 (0.13 – 171.97) (95% CI: 0.4–2.1)	6.97 (0.64 – 171.66) (95% CI: 3.5–10.4)	0.020

Data are presented as median (min-max); *p<0.05 : significant difference

Table 2 shows that the pre-PCNL IL-6 level in Group A was 0.75 pg/mL (range 0.13–7.68), while in Group B it was 4.00 pg/mL (range 0.31–96.4). The IL-6 data distribution in both

analgesic groups was non-normal and heteroscedastic. Therefore, logarithmic transformation was applied, and the data were re-tested for normality and homogeneity, which were confirmed. An independent t-test on the transformed data yielded a p-value of 0.001 (<0.05), indicating a significant difference in pre-PCNL IL-6 levels between the two groups, with Group A showing lower baseline IL-6 levels.

Post-PCNL IL-6 levels in Group A were 1.25 pg/mL (range 0.13–171.97) compared to 6.97 pg/mL (range 0.64–171.66) in Group B. The data remained non-normally distributed and non-homogeneous until logarithmic transformation was performed, which corrected these issues. An independent t-test showed a significant difference (p = 0.020), with Group A again displaying lower IL-6 levels.

Table 3. Comparison of IL-6 Changes Pre- and Post-PCNL Between Analgesic Groups

Groups*	IL-6 levels (pg/ml)	p-value
	Mean ± SD	
Group A	12.97 ± 43.80 (95% CI: –11.5 to 37.4)	0.787
Group B	26.84 ± 61.44 (95% CI: –6.2 to 59.9)	

Table 3 indicates that changes in IL-6 levels from pre- to post-PCNL between Groups A and B were not significantly different (p = 0.787, Mann-Whitney test).

The median IL-6 level before PCNL was significantly lower in Group A compared to Group B (0.75 pg/mL, 95% CI 0.3–1.2 vs 4.00 pg/mL, 95% CI 2.1–5.9; p = 0.001). Similarly, post-PCNL IL-6 levels were lower in Group A (1.25 pg/mL, 95% CI 0.4–2.1) than in Group B (6.97 pg/mL, 95% CI 3.5–10.4; p = 0.020). However, the change in IL-6 levels between groups was not statistically significant (Group A: 12.97 ± 43.80, 95% CI –11.5 to 37.4 vs Group B: 26.84 ± 61.44, 95% CI –6.2 to 59.9; p = 0.787)

Discussion

In this study, demographic and baseline clinical characteristics, including age, sex distribution, BMI, leukocyte count, ASA score, and surgical duration, were comparable between groups. This homogeneity indicates that the observed outcomes were less likely to be influenced by demographic differences, thereby strengthening the validity of the comparison between treatment groups.

The main finding of this study was that the addition of dexamethasone to an ibuprofen-paracetamol regimen did not significantly alter IL-6 level changes compared to ibuprofen-paracetamol alone. Although both pre- and post-PCNL IL-6 levels were lower in the dexamethasone group, the magnitude of change was not statistically significant. This suggests that the anti-inflammatory benefit of dexamethasone may be limited in the acute postoperative phase when combined with non-opioid analgesics.[6,7]

This study has several limitations. The relatively small sample size may have reduced statistical power to detect subtle differences. IL-6 levels were only measured once postoperatively (2 hours), which might not capture the peak cytokine response. The single-center design may also limit generalizability. In addition, although baseline comparability was achieved, unmeasured variables such as nutritional status or pre-existing inflammation could still act as residual confounders.

The findings suggest that ibuprofen and paracetamol may already provide sufficient

modulation of IL-6 in PCNL patients, and the routine addition of dexamethasone may not provide clinically significant benefit in this context. However, dexamethasone may still have potential value in other settings, such as when longer-term anti-inflammatory effects are required.[8,9,10] These results highlight the need for further trials with larger samples and multiple time-point cytokine measurements to determine the true clinical relevance of adding corticosteroids to multimodal analgesia.

Another important consideration is the potential influence of confounding variables. Although baseline characteristics such as age, sex, BMI, leukocyte count, ASA score, and surgical duration were statistically comparable between groups, unmeasured factors such as pre-existing systemic inflammation, nutritional status, or genetic variability in cytokine expression may still have influenced IL-6 levels. Despite the application of multivariate analysis to adjust for possible confounders, residual confounding cannot be fully excluded.

Moreover, bias related to the relatively small sample size, single-center design, and reliance on a single postoperative IL-6 measurement may have introduced residual bias. These limitations could reduce the generalizability of our findings and suggest the need for larger, multicenter studies with repeated biomarker measurements to confirm these results.

Conclusion

This study concludes that there is no statistically significant difference in IL-6 level changes between PCNL patients receiving a combination of ibuprofen, paracetamol, and dexamethasone and those receiving only ibuprofen and paracetamol. While dexamethasone has known anti-inflammatory potential, its additional effect on IL-6 levels in this setting was not demonstrated. Further longitudinal studies with larger samples are needed to validate these findings.

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Conflicts of Interest

The authors reports no conflict of interest.

Data Availability Statement

The datasets generated and/or analysed for this study are available from the corresponding author upon reasonable request.

Author's Contributions

The author confirms sole responsibility for all aspects of this manuscript, including the conception and design of the work; acquisition, analysis, and interpretation of data; drafting and critical revision of the article; and final approval of the version to be published. The author also agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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