COMPARATIVE RANDOMIZED CONTROLLED STUDY OF ANALGESIC EFFECT BETWEEN ORAL COMBINATION ANALGESIA AND INTRAVENOUS ANALGESIA IN PATIENTS UNDERGOING EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY AT PHRAMONGKUTKLAO HOSPITAL

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Abstract

Background: Extracorporeal Shockwave Lithotripsy (ESWL) is a widely used, noninvasive treatment for upper urinary tract stones. Despite its routine use, patients often experience significant pain during the procedure, and opioid-based analgesia such as intravenous fentanyl may lead to adverse effects. Optimizing pain control while minimizing opioid exposure remains a clinical challenge.

Objectives: To compare the analgesic efficacy and side effect profiles of three analgesic regimens during ESWL: intravenous fentanyl alone, a combination of oral and intravenous analgesics, and oral analgesics alone.

Methods: This randomized clinical trial included 78 ESWL sessions from 72 patients with renal or ureteric stones. Patients were randomized into three groups: Group A received intravenous fentanyl (50 µg); Group B received oral paracetamol (500 mg) and ibuprofen (400 mg) plus intravenous fentanyl (50 µg); Group C received oral tramadol (50 mg), paracetamol (500 mg), and ibuprofen (400 mg). A rescue dose of intravenous fentanyl 50 µg was offered when a patient reported an NRS score > 8 or was unable to tolerate the pain. The primary outcome was pain intensity, measured using the 11-point Numeric Rating Scale (NRS; 0 = no pain, 10 = worst possible pain), administered every 15 minutes during the procedure. Patients verbally rated their pain by choosing a number between 0 and 10. The secondary outcomes were the occurrence of adverse effects and the need for a rescue dose of intravenous fentanyl (50 µg, if NRS > 8 or intolerable pain). The stone-free rate was assessed at 2–4 weeks.

Results: Baseline characteristics were comparable between groups, except for body mass index. The mean pain scores were 6.39 ± 1.26 in Group A, 5.38 ± 1.85 in Group B, and 5.88 ± 1.34 in Group C. Group B reported significantly lower pain scores than Group A at 15 minutes (2.5 ± 1.96 vs. 3.77 ± 1.95, $p = 0.018$) and 30 minutes (4.73 ± 2.24 vs. 6.08 ± 1.81, $p = 0.016$). Group C had significantly lower pain scores at 60 minutes (6.73 ± 1.59 vs. 7.88 ± 1.99, $p = 0.034$) and 75 minutes (7 ± 1.39 vs. 7.94 ± 1.3, $p = 0.040$) compared to Group A. The incidence of adverse effects was lowest in Group C (dizziness: 23.1%). A rescue intravenous fentanyl dose was required among 6 (23.1%) of Group A, 6 (23.1%) of Group B, and 11 (42.3%) of Group C; these differences were not statistically significant.

Conclusion: Combining oral and intravenous analgesics offers superior early pain control during ESWL compared to intravenous fentanyl alone. Oral-only multimodal analgesia, with provision for a rescue intravenous fentanyl dose, administered when needed, provided comparable pain relief with fewer side effects and may reduce routine opioid use during ESWL. The inclusion and reporting of the rescue dose are essential for a consistent and practical analgesic strategy.

Keywords: procedural pain, analgesic pain medication, extracorporeal shockwave lithotripsy, oral analgesia, paracetamol, ibuprofen, tramadol, fentanyl

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Introduction

Kidney stones are among the most common urological conditions, with a lifetime prevalence ranging from 1% to 20%, depending on factors such as age, sex, ethnicity, and geographic location.[1] In Thailand, the incidence has been reported as high as 19%.[2] Among various treatment options, Extracorporeal Shockwave Lithotripsy (ESWL) is widely accepted as a first-line, noninvasive procedure for managing renal stones measuring less than 2 cm and ureteric stones measuring less than 1 cm, in accordance with the European Association of Urology (EAU) guidelines.[3]

ESWL is generally safe and effective, but the shockwaves used during treatment often cause moderate to severe pain. This discomfort may lead to involuntary patient movement, which can impair targeting and reduce the effectiveness of treatment.[4] Therefore, appropriate analgesia is essential to ensure both patient comfort and procedural efficacy. While general anesthesia is rarely used for this purpose, a variety of analgesic approaches—including injectable opioids, oral medications, and topical anesthetics—are currently employed.

To date, no standardized guidelines exist for optimal pain management during ESWL. Commonly used agents include nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ketorolac, and ibuprofen, as well as opioids like morphine, pethidine, and fentanyl.[5] These are often administered alone or in combination with sedative-hypnotics. Although intravenous opioids such as fentanyl are effective for rapid pain relief, they carry a risk of adverse effects, including respiratory depression, hypotension, dizziness, and nausea/vomiting, which may require additional monitoring and intervention.

Recent interest has shifted toward non-opioid analgesics with more favorable safety profiles. Paracetamol and tramadol have shown promise as alternative or adjunctive agents. Previous studies have suggested that intravenous or oral paracetamol may reduce the need for opioids during procedures like ESWL, while minimizing side effects.[6,7] However, evidence remains inconclusive, and the optimal analgesic regimen—balancing efficacy with tolerability—has yet to be clearly defined.

The objective of this study was to compare the analgesic efficacy and side effect profiles of three regimens used during ESWL: intravenous fentanyl alone, a combination of oral and intravenous analgesics, and oral analgesics alone. We hypothesized that multimodal oral analgesia, with or without intravenous fentanyl, could provide effective pain relief while minimizing opioid-related adverse effects.

Methods

The study protocol was approved by the Institutional Review Board of Phramongkutklao Hospital (IRBRTA 1044/2565). The open-label randomized clinical trial was conducted at the Division of Urology, Phramongkutklao Hospital, Bangkok, Thailand. The data was collected over one year, from December 2021 to December 2022. The study enrolled patients aged 18 years or older with upper urinary tract stones who were scheduled for Extracorporeal Shockwave Lithotripsy (ESWL).

Inclusion and exclusion criteria

Eligible participants included adults undergoing ESWL for renal stones ≤2 cm or ureteric stones ≤1 cm. Exclusion criteria were: estimated glomerular filtration rate (eGFR) <60 mL/min,

pregnancy, known allergy to any of the study medications, cognitive impairment or dementia, chronic analgesic dependence, and use of analgesic drugs on the day of the procedure.

Data collection

After written informed consent was obtained, baseline demographic and clinical data were recorded, including age, sex, body weight, height, body mass index (BMI), underlying comorbidities, renal function (eGFR), history of prior ESWL, and presence of ureteral stent. Stone characteristics were also documented, including size, location, Hounsfield units, and skin-to-stone distance.

Randomization and interventions

Written informed consent was obtained from all participants before their enrollment in the study. Participants were randomized using a computer-generated randomization list prepared by the author's colleague, who was not involved in patient care or outcome assessment. Block randomization with a block size of six was used to ensure balanced allocation across treatment groups. The randomization sequence was concealed in sequentially numbered, opaque, sealed envelopes, which were opened only after obtaining consent and confirming patient eligibility.

Due to the nature of the interventions, blinding of patients and treating physicians was not feasible. However, outcome assessors responsible for evaluating pain scores and other study endpoints were blinded to treatment allocation to minimize bias in their assessments.

Group A received intravenous fentanyl 50 µg, administered 10 minutes before the procedure. Group B received oral paracetamol 500 mg and ibuprofen 400 mg 30 minutes prior, plus intravenous fentanyl 50 µg 10 minutes before the procedure. Group C received oral tramadol 50 mg, paracetamol 500 mg, and ibuprofen 400 mg 30 minutes before the procedure.

Pain and safety assessment

Pain was assessed using the 11-point Numeric Rating Scale (NRS; 0 = no pain, 10 = worst possible pain), where patients verbally rated their pain by choosing a number between 0 and 10 that best described their current level of pain. NRS scores, systolic and diastolic blood pressure, and peripheral oxygen saturation were recorded at baseline and every 15 minutes during the ESWL procedure. Independent blinded assessors measured pain scores and monitored adverse events at 15-minute intervals. If a patient reported an NRS score > 8 or was unable to tolerate the pain, a rescue dose of intravenous fentanyl 50 µg was offered. Adverse events were continuously monitored and recorded at 15-minute intervals throughout the ESWL procedure. After the procedure was completed, each patient was observed for an additional hour in the recovery area, during which any adverse events were also documented.

Follow-up and outcome evaluation

Patients were followed up at 2 to 4 weeks after the procedure. Treatment outcomes were classified as: stone-free (no residual fragments), success (asymptomatic residual fragment ≤4 mm), or failure (symptomatic residual stone or obstructive complication).

Statistical Analysis

The sample size was calculated based on findings from a previous randomized study by Akcali et al., which demonstrated that intravenous paracetamol provided significantly better analgesia than lornoxicam and tramadol during ESWL, with a mean difference in pain scores of approximately 1.5 units on the Numeric Rating Scale (NRS).[6] Assuming a minimal clinically significant difference of 1.5, a standard deviation of 2.0, a statistical power of 80%, and a two-sided alpha level of 0.05, the required sample size was 21 patients per group.

All statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Pain assessors and data analysts were blinded to group allocation to minimize bias in the assessment. Continuous variables were expressed as mean ± standard deviation (SD), discrete variables as median (interquartile range) where appropriate, and categorical variables were reported as frequencies and percentages.

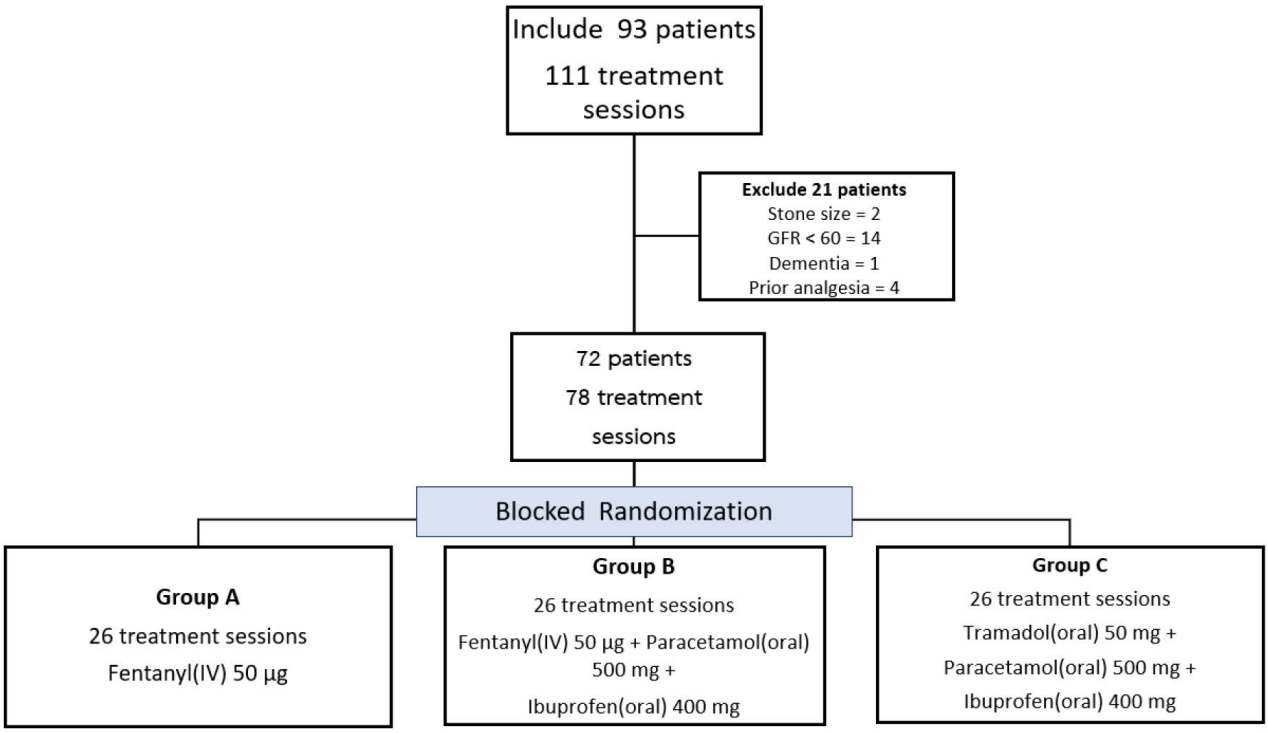

Figure 1. Consort flow diagram of the study

Because some patients underwent more than one ESWL session, resulting in repeated measures, a mixed-effects model was used for comparing primary and secondary outcomes, with patient identity included as a random effect to account for within-subject correlation. Categorical variables were compared using chi-square tests or mixed-effects logistic regression as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Results

Seventy-eight patients were included in the study and were divided into three groups (n = 26 per group). Of the subjects, 48 (70.5%) were male and 20 (29.5%) were female. The mean age of the patients was 54.64 ± 12.2 years. The mean stone size was 8.4. ± 3.93 mm. The baseline demographic characteristics were not significantly different across all three groups, except for BMI, which was lower in Group B (23.3 ± 3.38) compared to both Group A (26.2 ± 3.49) and Group C (25.63 ± 4.35). **Table 1** shows demographic data of the participants.

The pain scores measured by the NRS at 15 minutes in groups A, B, and C were 3.77 ± 1.95, 2.5 ± 1.96, and 3.58 ± 1.77, respectively. There was statistical significance between the three groups (p = 0.039). Group B had a significantly lower pain score compared to both groups A (p = 0.018) and C (p = 0.044)

At 30 minutes, the pain scores in Groups A, B, and C were 6.08 ± 1.81, 4.73 ± 2.24, and 5.58 ± 1.81, respectively. Statistically significant differences were observed among the three groups (p = 0.05). Group B had a significantly lower pain score compared to Group A (p = 0.016). There were no statistically significant differences between Groups A and C or between Groups B and C.

At 45 minutes, the pain scores in Groups A, B, and C were 7 ± 1.67, 6.08 ± 2.15, and 6.5 ± 1.68, respectively. However, no statistically significant differences were observed among the three groups (p = 0.204).

At 60 minutes, the pain scores in Groups A , B and C were 7.88 ± 1.99, was 7 ± 2.08, and 6.73 ± 1.59. There was no statistically significant difference between the three groups (p = 0.085). However, using post-hoc analysis, Group C had a significantly lower pain score compared to Group A (p = 0.034).

Table 1. Demographic data of participants

	Group A (n=26)	Group B (n=26)	Group C (n=26)	*p*-value
Sex (Male)	15 (57.7%)	17 (65.4%)	16 (61.5%)	0.850
Age	55.65 ± 13.65	50.46 ± 10.65	57.81 ± 12.62	0.096
Body Weight	67.38 ± 11.48	63 ± 8.96	68.92 ± 11.9	0.132
Height	160.23 ± 8.34	164.73 ± 7.76	164.15 ± 8.84	0.113
BMI	26.2 ± 3.49	23.3 ± 3.38	25.63 ± 4.35	0.016
Serum Creatinine	0.97 ± 0.2	0.91 ± 0.23	0.91 ± 0.2	0.513
Prior ESWL, Yes	4 (15.4%)	7 (26.9%)	5 (19.2%)	0.577
Imaging Modality				0.694
CT scan	15 (57.7%)	16 (61.5%)	13 (50%)	
Film x-ray	11 (42.3%)	10 (38.5%)	13 (50%)	
Stone size (mm)	8 ± 3.15	8.87 ± 4.5	8.37 ± 4.15	0.730
Side				0.374
left	14 (53.8%)	12 (46.2%)	17 (65.4%)	
Right	12 (46.2%)	14 (53.8%)	9 (34.6%)	
Stone location				0.700
Distal ureter	2 (7.7%)	1 (3.8%)	0 (0%)	
Lower pole	6 (23.1%)	10 (38.5%)	5 (19.2%)	
Middle pole	4 (15.4%)	2 (7.7%)	6 (23.1%)	
Mid ureter	1 (3.8%)	0 (0%)	0 (0%)	
Renal pelvis	3 (11.5%)	5 (19.2%)	5 (19.2%)	
upper pole	3 (11.5%)	3 (11.5%)	3 (11.5%)	
upper ureter	7 (26.9%)	5 (19.2%)	7 (26.9%)	
Hounsfield unit	930.8 ± 336.39	889.48 ± 355.14	864.62 ± 299.91	0.868
Skin-to-Stone Distance	9.21 ± 2.02	8.57 ± 1.96	9.96 ± 2.51	0.239
infundibulopelvic angle	80 ± 7.07	74.29 ± 10.97	77.5 ± 10.61	0.612
Ureteric stent, yes	7 (26.9%)	8 (30.8%)	8 (30.8%)	0.940
Number of Shots	4923.08 ± 271.75	4923.08 ± 392.23	5000 ± 0	0.512
Mean Energy	1.85 ± 0.39	1.93 ± 0.35	2.17 ± 0.36	0.006
Time (min)	70.19 ± 7	69.62 ± 10.58	75.38 ± 3.72	0.014
Follow-up (day)	17.42 ± 6.44	17.38 ± 4.86	16.04 ± 5.15	0.591

Abbreviations
Group A fentanyl alone
Group B paracetamol + ibuprofen + fentanyl
Group C tramadol + paracetamol + ibuprofen
Values are represented as mean_SD.
p-value by Chi-square test and ANOVA test

At 75 minutes, the pain scores in Groups A, B, and C were 7.94 ± 1.3, 7.57 ± 1.6, and 7 ± 1.39, respectively. Statistically significant differences were observed among the three groups (p = 0.105). However, using post-hoc analysis, group C had a significantly lower pain score compared to group A (p = 0.040).

The number of patients who received a rescue dose was highest in Group C(12) but there was no statistically significant difference compared to Groups A (6) and B (6). The outcomes, defined as stone-free, success (asymptomatic residual stone of <4 mm), and failure, were also not statistically significant in all three groups. The incidence of

Table 2. Primary Outcomes: Comparisons of Mean Numeric Rating Scale (NRS) Scores

Pain Score	Group A (n=26)	Group B (n=26)	Group C (n=26)	*p*-value			
				3 groups	A vs B	A vs C	B vs C
Pain at 15 Minutes	3.77 ± 1.95	2.5 ± 1.96	3.58 ± 1.77	0.039	0.018	0.716	0.044
Pain at 30 Minutes	6.08 ± 1.81	4.73 ± 2.24	5.58 ± 1.81	0.050	0.016	0.362	0.125
Pain at 45 Minutes	7 ± 1.67	6.08 ± 2.15	6.5 ± 1.68	0.204	0.076	0.333	0.412
Pain at 60 Minutes	7.88 ± 1.99	7 ± 2.08	6.73 ± 1.59	0.085	0.102	0.034	0.610
Pain at 75 Minutes	7.94 ± 1.3	7.57 ± 1.6	7 ± 1.39	0.105	0.434	0.040	0.181
Mean Pain	6.39 ± 1.26	5.38 ± 1.85	5.88 ± 1.34	0.074	0.023	0.215	0.259

Abbreviations
Group A fentanyl alone
Group B paracetamol + ibuprofen + fentanyl
Group C tramadol + paracetalmol + ibuprofen
Values are represented as mean_SD.
p-value by Chi-square test and ANOVA test

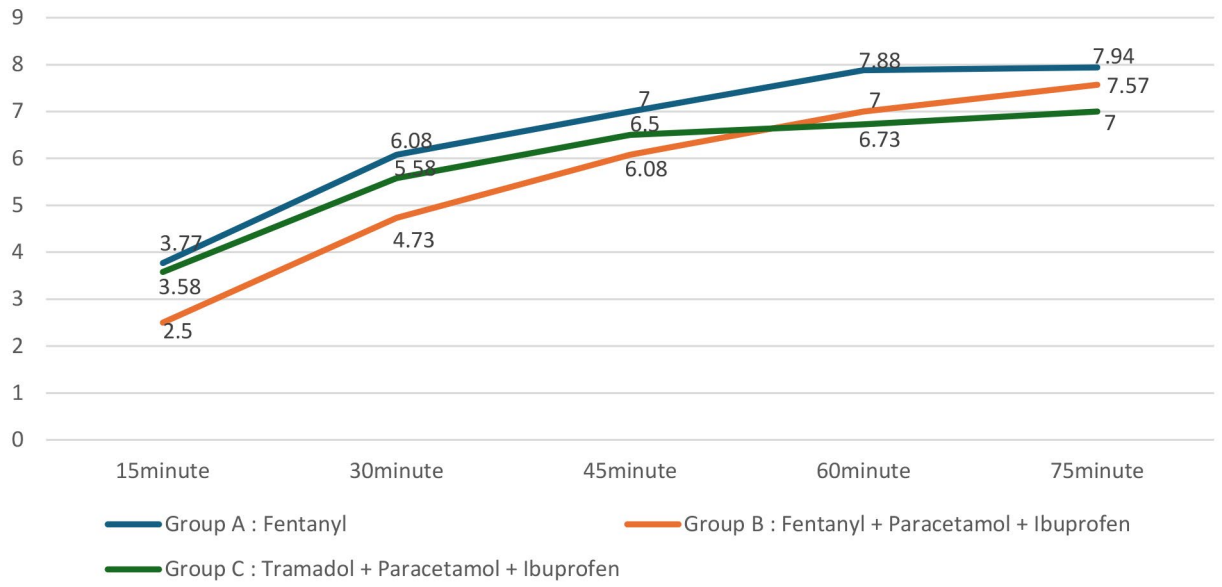

Figure 2. Primary Outcome (Pain Score)

Table 3. Secondary Outcomes: Occurence of Adverse Effects and the Need for a Rescue Dose of Intravenous Fentanyl

	Group A (n=26)	Group B (n=26)	Group C (n=26)	*p*-value			
				3 Groups	A vs B	A vs C	B vs C
Rescue Dose	6 (23.1%)	6 (23.1%)	11 (42.3%)	0.214	1	0.139	0.139
Median Time of Rescue Dose (Minute)(IQR)	45(15)	45(0)	45(15)	1			
Mean Total Fentanyl Dosage (Microgram)(SD)	73(21.08)	73(21.08)	21(24.64)	<0.001	1	<0.001	<0.001
Outcome				0.998	1	0.948	0.948
Fail	11 (42.3%)	11 (42.3%)	10 (38.5%)				
Stone Free	8 (30.8%)	8 (30.8%)	9 (34.6%)				
Success	7 (26.9%)	7 (26.9%)	7 (26.9%)				
Side Effect							
Nausea, Vomiting	4 (15.4%)	5 (19.2%)	1 (3.8%)	0.225	0.714	0.158	0.083
Dizziness	13 (50%)	12 (46.2%)	6 (23.1%)	0.100	0.781	0.044	0.080
Hypotension	1 (3.8%)	1 (3.8%)	0 (0%)	0.599	1	0.313	0.313
Bradycardia	1 (3.8%)	2 (7.7%)	0 (0%)	0.353	0.552	0.313	0.149
Respiratory Depression	0 (0%)	0 (0%)	0 (0%)				

Abbreviations
Group A fentanyl alone
Group B paracetamol + ibuprofen + fentanyl
Group C tramadol + paracetalmol + ibuprofen
Values are represented as mean_SD.
p-value by Chi-square test and ANOVA test

dizziness, nausea, and vomiting was lowest in Group C, but there was no statistical significance.

Sensitivity analyses adjusting for BMI yielded similar results. For example, at 15 minutes, Group B remained significantly lower in NRS (adjusted mean difference and 95% CI reported in **Table 2**) compared to Group A. At 60 and 75 minutes, the difference between Group C and Group A remained significantly lower. No conclusions changed after BMI adjustment.

Discussion

This randomized study demonstrated that combining oral paracetamol and ibuprofen with intravenous fentanyl provides superior early analgesic efficacy during ESWL compared to intravenous fentanyl alone or oral analgesics alone. Specifically, Group B (oral NSAIDs plus IV fentanyl) had significantly lower pain scores at 15 minutes, while Group C (oral tramadol, paracetamol, and ibuprofen) showed superior pain control at later stages (60 and 75 minutes). In contrast, patients receiving only intravenous fentanyl (Group A) consistently reported higher pain scores throughout the procedure.

Fentanyl remains a highly potent opioid analgesic with the advantage of rapid onset when administered intravenously. Following injection, its analgesic effect begins almost immediately, with peak efficacy achieved within 5 to 15 minutes. However, its relatively short duration of action—typically lasting between 30 and 60 minutes—can limit its utility for procedures with longer or fluctuating pain profiles.[10,11] This pharmacokinetic profile necessitates careful plan-

ning when integrating fentanyl into multimodal analgesic regimens, especially for interventions like ESWL that may extend beyond this window of maximal analgesic activity.

When comparing fentanyl's pharmacodynamics with pain patterns during ESWL, a notable discrepancy was observed. While intravenous fentanyl provides immediate analgesia with peak effect at 5–15 minutes, its duration (30–60 minutes) did not align well with the typical pain trajectory of ESWL, where pain intensity frequently became more pronounced after 30 to 45 minutes.[5,6] In this study, patients in Group A—who received only intravenous fentanyl—tended to have the highest pain scores as the procedure progressed. Notably, although 15 patients (57% of Group A) experienced severe pain (pain scores >8) and were offered an additional dose of intravenous fentanyl, only six accepted. The majority declined further fentanyl, citing adverse effects such as dizziness and nausea/vomiting as the primary reason for refusal. This finding is consistent with the literature reporting that opioid-related side effects often limit their tolerability and repeated use during procedures.[9]

Paracetamol and ibuprofen, both commonly used in multimodal analgesia, have an onset of action of approximately 30 minutes following oral administration. In this study, Group B patients—who received paracetamol and ibuprofen in addition to intravenous fentanyl—experienced enhanced overall analgesic efficacy compared to those receiving fentanyl alone. This supports the synergistic effect of combining non-opioid analgesics with opioids, as highlighted in multiple studies.[5,12] However, it is essential to note that, despite improved pain control, a significant number of patients in Group B continued to experience opioid-related side effects such as nausea and dizziness, similar to trends reported in previous literature.[9,12]

In this study, the group receiving only the oral combination of paracetamol, ibuprofen, and tramadol demonstrated analgesic efficacy that was comparable to the group receiving intravenous fentanyl alone. Notably, the incidence of adverse effects in the oral-only group was substantially lower. Only one out of twelve patients in this group reported a side effect. Subsequently, they refused an additional dose of intravenous fentanyl, in contrast to the higher rate of opioid-related side effects observed in groups receiving intravenous fentanyl. These findings are consistent with published literature indicating that multimodal oral analgesic regimens can provide effective pain control with a reduced risk of opioid-related complications.[5,9,12] The results support the consideration of oral combination analgesia as a viable and potentially safer alternative for ESWL pain management, particularly in ambulatory or outpatient settings.

Combining these oral analgesics (paracetamol, ibuprofen, and tramadol) resulted in significantly lower pain scores at both 60 and 75 minutes compared to the group that received intravenous fentanyl alone; this suggests that the multimodal oral regimen not only provides comparable immediate analgesic efficacy but also offers a more sustained analgesic effect throughout longer procedures such as ESWL. These findings align with previous research indicating the benefits of multimodal analgesia in extending pain control and reducing opioid consumption and side effects.[13]

These findings align closely with prior research. Akcali et al. found that paracetamol was significantly effective for ESWL analgesia, with no difference in supplemental analgesic use between groups.[6] Similarly, Eker et al. demonstrated that intravenous paracetamol effectively reduced sedative requirements during pediatric ESWL procedures.[7] NSAIDs, through inhibition of prostaglandin synthesis, have been shown to provide adequate analgesia via various routes and are associated with fewer side effects compared to opioids, particularly in terms of hemodynamic and respiratory stability.[8] The concept of multimodal analgesia—combining opioid and non-opioid agents—has been widely advocated to optimize pain control while minimizing opioid burden.[9]

Our results align with the growing body of evidence supporting multimodal analgesic strategies for ESWL. For instance, Fredman et al.[14] reported that NSAIDs, when combined with opioids, significantly reduced both pain scores

and opioid requirements, mirroring our findings that group B exhibited superior early analgesia compared to IV fentanyl alone. In addition, systematic reviews by Choudhary et al.[15] further corroborate the effectiveness of oral NSAIDs, paracetamol, and tramadol, consistent with our observation of sustained pain relief and fewer side effects in the oral-only group (Group C).

Our results support this approach. The concurrent use of oral paracetamol and ibuprofen in Group B enhanced the early analgesic effect of IV fentanyl. However, this group still experienced a notable rate of opioid-related side effects. In contrast, the oral-only regimen (Group C) offered sustained pain control in the later phase of the procedure with the lowest incidence of adverse effects. The delayed onset of oral tramadol likely explains the higher pain scores in this group during the first 15 minutes. Despite this, only one patient in the oral-only group required rescue fentanyl, which was declined due to concern about side effects.

Importantly, in our protocol, the rescue dose of intravenous fentanyl was typically administered around 45 minutes into the procedure (median of 45 minutes), coinciding with the time frame when pain intensity characteristically increases during ESWL. This timing reflects real-world practice and underscores the strategic use of fentanyl for breakthrough pain, further supporting the multimodal approach where early analgesia is managed with oral agents and a rescue opioid is reserved for later, higher pain periods.

Our study suggested that administering a combination of oral analgesics 30 minutes before ESWL, with a rescue dose of intravenous fentanyl as needed (median 45 minutes into the procedure), offers superior pain control compared to intravenous fentanyl alone. Notably, this regimen showed a trend toward better pain control than the oral paracetamol plus ibuprofen and IV fentanyl group (Group B) after 60 minutes. However, this difference did not reach statistical significance, potentially due to the limited sample size. Further studies with larger cohorts may be needed to confirm this observation. Adopting this multimodal analgesia protocol may optimize patient comfort and safety during ESWL.

This study showed several strengths, including its randomized controlled design, standardized ESWL protocol, and objective pain assessment at multiple time points. It also reflects real-world practice by comparing opioid-based and non-opioid regimens, contributing to practical multimodal pain management strategies.

However, the study encountered some limitations. The single-center setting and open-label design limited external validity and introduced performance bias. The small sample size might have limited the power to detect differences in adverse events, and the imbalance in BMI across groups could have influenced analgesic metabolism. Although sensitivity analyses were performed, future studies with larger cohorts and stratified randomization are warranted.

Despite these limitations, the findings are likely generalizable to other tertiary care or outpatient settings. The oral-only analgesic regimen represents a feasible alternative to intravenous opioids, particularly in resource-limited environments where minimizing intravenous interventions is advantageous.

Future studies should focus on optimizing the timing of intravenous fentanyl administration in combination with oral analgesics to determine whether earlier or adjusted dosing can further improve early-phase pain control while minimizing side effects. Additionally, comparative studies evaluating oral combination analgesia with a protocolized rescue dose versus routine opioid use would help clarify the most effective and safest approach for ESWL pain management. Large-scale, randomized controlled trials are warranted to assess not only analgesic efficacy and safety, but also patient satisfaction, resource utilization, and cost-effectiveness of various multimodal regimens. Furthermore, investigating patient-specific factors—such as comorbidities, pain thresholds, and pharmacogenomics—may help tailor analgesic strategies for individualized care.

Conclusion

This study demonstrated that a multimodal regimen—administering a combination of oral

paracetamol, ibuprofen (with or without tramadol) 30 minutes before ESWL, supplemented by a rescue dose of intravenous fentanyl given as needed at a median of 45 minutes into the procedure—provided more effective and sustained pain control than intravenous fentanyl alone. Although the oral-only regimen showed a trend toward superior pain control compared to the regimen including IV fentanyl after 60 minutes, this difference was not statistically significant, highlighting the need for larger studies. We recommend adopting an oral multimodal analgesic protocol, with rescue fentanyl as needed, to optimize patient comfort and minimize opioid-related side effects during ESWL.

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