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Research Article

Short-term perfusion and respiratory effects of dexketoprofen, tramadol, and their combination in renal colic: A prospective randomized capnography study

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ABSTRACT

Objective: Intravenous non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, including dexketoprofen trometamol and tramadol, remain the primary analgesic options for treating acute renal colic in emergency departments. However, concerns about respiratory depression associated with opioids can limit the use of tramadol with confidence, and there are limited data on the short-term respiratory and perfusion effects of these agents. The present study aimed to evaluate the short-term effects of intravenous dexketoprofen trometamol, tramadol, and their combination on tissue perfusion and respiratory function. The study assessed these effects using EtCO₂ and related physiological parameters. The study population comprised hemodynamically stable emergency department patients presenting with acute renal colic.

Methods: In this prospective, randomized, controlled trial conducted in an academic emergency department, adults aged 18–55 with acute renal colic received one of three intravenous regimens: dexketoprofen trometamol (50 mg), tramadol (100 mg), or their 50 mg/50 mg combination. Vital signs, SpO₂, and EtCO₂ were recorded at baseline, 30, and 60 minutes; arterial blood gases, including lactate, were drawn at baseline and 60 minutes. The primary endpoint of the study was the EtCO₂ trajectory over time.

Results: In a study of 102 patients (with 34 patients in each group), EtCO₂, heart rate, and blood pressure were found to be similar between the groups at all measured time points. Furthermore, analysis using mixed-effects models revealed no significant group-by-time interactions. SpO₂ levels were found to be lower in the combination group compared to the dexketoprofen group at the 60-minute mark (93.8% vs. 95.4%; ANOVA $p = 0.018$; post hoc $p = 0.016$). In the present study, seven patients, all in tramadol-containing arms, exhibited transient SpO₂ levels below 90%, though none of these patients required oxygen supplementation. The blood-gas parameters demonstrated stability, while lactate levels exhibited a significant decrease across all groups, without any observed between-group variation.

Conclusion: In patients with renal colic who were hemodynamically stable, the three treatment plans resulted in similar short-term effects on EtCO₂, hemodynamics, and blood-gas parameters. The findings of this study demonstrate that modest SpO₂ declines, accompanied by transient desaturations in the tramadol-containing arms, provide substantiated support for the implementation of pulse oximetry and capnography monitoring when tramadol is administered. It should be noted that the study was not designed to assess comparative safety, and thus the findings should be considered physiological observations only. The lactate reduction may be indicative of a resolution of pain-related stress; however, this remains a hypothesis that requires further investigation.

Trial Registration: The study was registered at ClinicalTrials.gov (ID: NCT07386288). Registration was retrospective.

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1. Introduction

Acute renal colic is a prevalent cause of emergency department visits, characterized by its intense and debilitating pain. Patients frequently report it to be one of the most severe pain experiences they have ever endured. The majority of cases are attributable to an obstructing ureteral stone, which leads to elevated intraluminal pressure, the occurrence of ureteral spasm, and the stimulation of visceral nociceptors. The resultant flank pain is often accompanied by symptoms such as nausea, vomiting, and agitation [1,2]. Given its high prevalence among young and middle-aged adults, renal colic constitutes a substantial clinical and operational burden for emergency departments worldwide [3,4]. Consequently, the provision of rapid and effective analgesia constitutes a fundamental element of initial management.

Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics remain the principal pharmacological options for the management of acute renal colic [5–7]. The analgesic effect of NSAIDs is primarily attributable to their capacity to inhibit cyclooxygenase-mediated prostaglandin synthesis, a process that results in a reduction in ureteral smooth muscle tone, intrarenal pressure, and inflammatory-mediated pain [5]. A substantial body of research, encompassing numerous systematic reviews and meta-analyses, has demonstrated the analgesic efficacy of parenteral NSAIDs to be comparable to, and in some cases superior to, that of opioids. Furthermore, these studies have shown that parenteral NSAIDs are associated with reduced rates of vomiting and a decreased requirement for rescue analgesia [3,6–9]. Opioids remain a treatment of choice when NSAIDs are contraindicated or insufficient. Contemporary guidance, including the European Association of Urology recommendations and NICE guideline NG118, positions NSAIDs as first-line analgesia when not contraindicated, with opioids such as tramadol reserved for second-line or rescue use; the present study therefore evaluated tramadol both alone and in combination with dextketoprofen as a physiological safety comparison rather than as a first-line efficacy recommendation [3,10]. However, conventional opioids are associated with well-recognised adverse effects, including nausea, vomiting, respiratory depression, and dependence. Tramadol, a synthetic opioid with weak μ -opioid receptor agonism and additional monoaminergic activity, is often considered an intermediate option with a more favourable respiratory safety profile compared with stronger opioids. Dextketoprofen trometamol, the active S(+)-enantiomer of ketoprofen, is a rapidly acting NSAID that has demonstrated efficacy and good tolerability in the intravenous treatment of acute pain, including renal colic [9,11]. Despite the extensive literature comparing the analgesic efficacy and adverse-event profiles of these agents, data regarding their short-term effects on systemic hemodynamics and tissue perfusion are limited. It is acknowledged that acute pain itself is known to increase sympathetic activity, elevate heart rate and blood pressure, and alter regional blood flow. Conversely, effective analgesia has been demonstrated to attenuate these responses. However, sedative or opioid-based therapies have been demonstrated to impair ventilation and gas exchange [12].

EtCO₂, measured noninvasively via capnography, reflects the integrated relationship between ventilation, cardiac output, and carbon dioxide production. It has been proposed as a surrogate marker of global tissue perfusion. Reduced EtCO₂ levels have been demonstrated to be associated with decreased cardiac output, elevated lactate concentrations, and adverse outcomes in critically ill patients. Nevertheless, the clinical usefulness of EtCO₂ in detecting more subtle perfusion changes during analgesic treatment in hemodynamically stable ED patients remains unclear [13–15]. To the best of our knowledge, no prospective randomised study has specifically evaluated the effects of intravenous dextketoprofen trometamol, tramadol, or their combination on EtCO₂ and other physiological markers of tissue perfusion in spontaneously breathing patients presenting with renal colic. The primary objective of this study was therefore to compare the short-term effects of these three analgesic regimens on EtCO₂, vital signs, and arterial blood-gas parameters, including lactate, in adult ED patients with renal colic. It was hypothesised that none of the three regimens would induce clinically significant changes in EtCO₂ or other global perfusion and respiratory surrogates during the first hour of treatment.

Beyond its established role as a global perfusion surrogate, EtCO₂ has increasingly been recognized as an early, continuous, and non-invasive indicator of opioid-induced ventilatory impairment, capable of detecting hypoventilation before changes become apparent on pulse oximetry [16,17]. In emergency department settings where opioids such as tramadol are administered alongside NSAIDs for acute pain, this early-warning capacity has direct relevance to bedside safety monitoring, independent of any demonstrable perfusion effect. The evaluation of EtCO₂ trajectories following dextketoprofen trometamol, tramadol, and their combination is a pragmatic approach to addressing a salient safety concern. This concern pertains to the question of whether commonly utilized ED analgesic regimens carry any discernible respiratory risk signal. This approach diverges from conventional testing methods that focus exclusively on perfusion physiology.

2. Materials and Methods

2.1. Study design and setting

This prospective, randomized, single-center study was conducted in the emergency department of Atatürk University Faculty of Medicine, Yakutiye Research Hospital, Erzurum, Türkiye between November 2024 and April 2025; the first participant was enrolled on 10 November 2024. Adults aged 18–55 years presenting with flank pain and a clinical and imaging-confirmed diagnosis of renal colic were eligible. The study received approval from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Decision No. 2024-16/01, dated 7 November 2024), and written informed consent was reported for all enrolled participants. The trial was registered retrospectively at ClinicalTrials.gov (NCT07386288; first submitted on 20 January 2026).

In order to qualify for inclusion in the study, patients

were required to have a Glasgow Coma Scale score of 15, intact spontaneous breathing, and the ability to give informed consent themselves. Individuals who met any of the following criteria were excluded from the study: those who were pregnant or breastfeeding, those with chronic kidney or respiratory disease, those with a known allergy to any of the study drugs, those with hemodynamic instability, those with acute intoxication, those with poorly controlled epilepsy, or those who had recently taken a monoamine oxidase inhibitor.

2.2. Randomisation and interventions

The randomisation process employed a sealed-envelope technique, wherein equal numbers of opaque envelopes, labelled 1–3 (one per treatment arm), were prepared by a physician not involved in treatment administration and drawn sequentially by the treating physician. This ensured allocation concealment and balanced group sizes. The administration of the study drugs was conducted via intravenous infusions, with each infusion being administered over a period of 20 minutes. Utilising a 1:1:1 randomisation scheme, participants were assigned to receive one of three intravenous treatments: dexketoprofen trametamol 50 mg as an individual treatment, tramadol 100 mg as a standalone treatment, or a combination of both drugs at a ratio of 50 mg and 50 mg, respectively. Prior to infusion, each dose was diluted in 100 mL of normal saline. In the event that the treating physician deemed it necessary, intravenous morphine (5 mg) could be administered as rescue analgesia. Participants were blinded to treatment allocation, as all regimens were diluted in 100 mL of normal saline and administered as identical-appearing infusions; the physician who ordered the treatment and the nurse who prepared the infusions were not blinded.

2.3. Data collection and monitoring

The following parameters were recorded: blood pressure, heart rate, oxygen saturation, and EtCO₂. These were recorded at three time points: baseline (T0), 30 minutes (T30), and 60 minutes (T60). Arterial blood gases were only drawn at T0 and T60. The primary outcome of the study was the change in EtCO₂ over time, with vital signs and blood gas trajectories designated as secondary outcomes. It is notable that no participant received supplemental oxygen during the observation period, and no concomitant analgesics other than rescue morphine were administered.

The primary outcome was defined as the pattern of EtCO₂ change across T0, T30, and T60, which was then compared between the three analgesic arms. The continuous monitoring of EtCO₂ was conducted using a Nihon Kohden Vismo bedside monitor, with the sampling cannula employed for this purpose being of the sidestream nasal type. This was undertaken as an indirect measure of global perfusion. The secondary outcomes encompassed the time-course of heart rate, blood pressure, and SpO₂; the shift in arterial blood gas values (pH, bicarbonate, PCO₂, lactate, base deficit) from T0 to T60; and the comparison of these physiological responses across the treatment groups.

2.4. Sample size and statistical analysis

The required sample size was calculated using G*Power based on a previous study comparing the respiratory effects of tramadol and oxycodone [18], in which EtCO₂ was 45 ± 4 mmHg before and 43 ± 4 mmHg after administration. To detect a within-group difference of 2 mmHg (SD 4 mmHg; effect size $d_z = 0.5$) using a two-tailed paired *t* test with an alpha level of 0.05 and 80% power, 34 patients per arm were required, for a total of 102 patients.

All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.; Armonk, NY, USA). The normality of the data was checked using both a histogram inspection and the Shapiro–Wilk test. Continuous variables were reported as the mean $\pm$ standard deviation or as the change over time, and categorical variables were reported as counts with percentages. The alterations in vital signs and blood-gas measures within and between the groups were subjected to analysis using a repeated-measures ANOVA, while the between-group disparities were assessed through the implementation of a one-way ANOVA, complemented by Tukey post hoc comparisons. Paired *t* tests were used to analyze within-group T0-to-T60 comparisons, and categorical data were analyzed with χ^2 tests. For the purpose of this study, a *p* value of less than 0.05 was taken to indicate statistical significance.

As a sensitivity analysis, EtCO₂, heart rate, systolic and diastolic blood pressure, and SpO₂ were additionally re-analyzed using linear mixed-effects models with group, time, and group $\times$ time interaction as fixed effects and a random intercept for participant, in order to directly evaluate the group $\times$ time interaction for each repeatedly measured parameter. The analysis population comprised all randomized participants, with no post-randomization exclusions and no missing data at any timepoint.

3. Results

3.1. Participant characteristics

A total of 102 patients were enrolled in the study and randomly assigned equally to one of three treatment groups ($n = 34$ per group). The baseline sociodemographic and clinical characteristics of the patients are presented in Table 1.

Across the three designated time points (T0, T30, and T60), no statistically significant between-group disparities were observed in EtCO₂, heart rate, systolic or diastolic blood pressure. The study found that SpO₂ levels were comparable between the groups at T0 ($p = 0.584$) and T30 ($p = 0.635$). However, a statistically significant between-group variation was observed at T60 (one-way ANOVA, $F = 4.19$, $p = 0.018$). Further post-hoc Tukey testing revealed that this variation was attributable to the combination group compared to the dexketoprofen group ($93.82 \pm 2.02\%$ vs. $95.44 \pm 2.64\%$, $p = 0.016$). No pairwise comparison involving the tramadol group reached significance. Nineteen patients (Group 1: $n = 4$, Group 2: $n = 9$, Group 3: $n = 6$) had at least one SpO₂

measurement below 92% during the observation period, and seven patients (Group 2: $n = 4$, Group 3: $n = 3$) had at least one measurement below 90%. No patient received supplemental oxygen or required a respiratory intervention. Subsequent within-group analyses revealed no significant alterations in EtCO₂ across any of the study arms. However, a significant decrease in heart rate and systolic and diastolic blood pressure was observed from T0 to T30 in all three groups, with no further alterations between T30 and T60. The study revealed a transient decrease in SpO₂ at T30 in the dexketoprofen group ($p = 0.024$), with a subsequent return to the baseline level by T60 ($p = 0.932$ vs. T0). In the tramadol group, a decrease in SpO₂ was observed at T30 ($p = 0.009$), with a persistent lower level recorded at T60 ($p = 0.004$). In the combination group, a significant decrease in SpO₂ was noted

at T60 ($p = 0.003$). The hemodynamic values remained within clinically acceptable ranges throughout the observation period (see Table 2 and Figs. 1 and 2).

A sensitivity analysis using linear mixed-effects models confirmed these findings: no statistically significant group $\times$ time interaction was observed for EtCO₂, heart rate, systolic blood pressure, diastolic blood pressure, or SpO₂ (likelihood-ratio test, all $p \geq 0.24$), indicating that the trajectories of these parameters did not differ meaningfully between treatment groups over the observation period. A significant main effect of time was evident for heart rate, systolic and diastolic blood pressure, and SpO₂ (all $p < 0.001$), reflecting a decline associated with analgesia across all three groups equally; no significant main effect of group was found for any parameter (Fig. 3).

Table 1. Baseline demographic and clinical characteristics of the study population.

Variable		Group 1 ($n = 34$)	Group 2 ($n = 34$)	Group 3 ($n = 34$)	p value
Age (years), mean $\pm$ SD		34.7 $\pm$ 10.3	36.8 $\pm$ 10.2	35.5 $\pm$ 9.4	0.697
Sex, n (%)	Male	22 (64.7)	17 (50.0)	29 (85.3)	0.008
	Female	12 (35.3)	17 (50.0)	5 (14.7)	
History of stone passage, n (%)	Yes	20 (58.8)	23 (67.6)	26 (76.5)	0.298
	No	14 (41.2)	11 (32.4)	8 (23.5)	
Family history of nephrolithiasis, n (%)	Yes	21 (61.8)	18 (52.9)	20 (58.8)	0.755
	No	13 (38.2)	16 (47.1)	14 (41.2)	
Analgesic use in previous 24 h, n (%)	Yes	13 (38.2)	11 (32.4)	12 (35.3)	0.879
	No	21 (61.8)	23 (67.6)	22 (64.7)	

Group 1: 50 mg dexketoprofen; Group 2: 100 mg tramadol; Group 3: 50 mg dexketoprofen + 50 mg tramadol

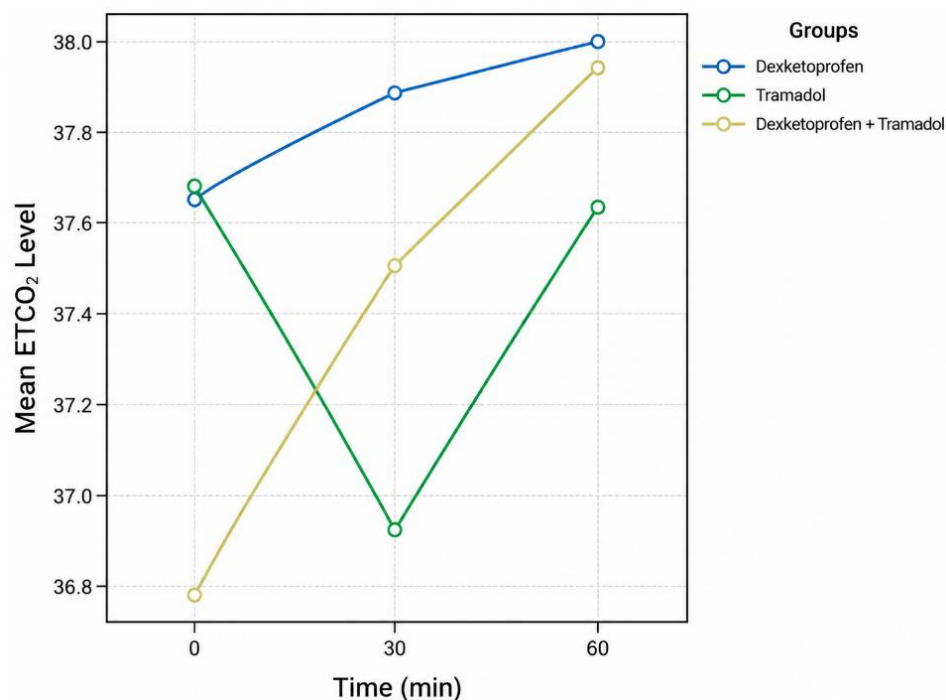


Fig. 1. Changes in end-tidal carbon dioxide levels over time; mean end-tidal carbon dioxide (EtCO₂) values measured at baseline (T0), 30 minutes (T30), and 60 minutes (T60) following intravenous administration of dexketoprofen, tramadol, or their combination. EtCO₂ levels remained within a narrow physiological range across all treatment groups throughout the observation period, with no evidence of clinically relevant deterioration in ventilation or global perfusion.

Table 2. Comparison of perfusion-related vital signs between treatment groups.

	Group 1 (n = 34)		Group 2 (n = 34)		Group 3 (n = 34)	
		p value		p value		p value
End-tidal CO ₂ (mmHg)						
T0	37.65 ± 3.65	0.820	37.68 ± 3.21	0.345	36.76 ± 4.02	0.182
T30	37.88 ± 4.15		36.91 ± 3.60		37.50 ± 2.94	
T60	38.0 ± 3.67		37.65 ± 4.17		37.94 ± 4.04	
Heart rate (beats/min)						
T0	86.50 ± 12.17	0.035 ^a	85.32 ± 14.60	< 0.001 ^a	82.29 ± 13.28	0.002 ^a
T30	81.53 ± 12.70	0.003 ^b	77.26 ± 11.29	0.001 ^b	76.56 ± 11.18	0.004 ^b
T60	80.32 ± 10.95	1.0 ^c	77.44 ± 12.30	1.0 ^c	75.91 ± 11.53	1.0 ^c
Systolic BP (mmHg)						
T0	131.68 ± 14.79	0.001 ^a	130.53 ± 15.31	0.004 ^a	130.53 ± 15.64	< 0.001 ^{a,b}
T30	122.53 ± 12.85	< 0.001 ^b	121.15 ± 16.66	< 0.001 ^b	119.06 ± 13.63	1.0 ^c
T60	122.71 ± 10.92	1.0 ^c	117.82 ± 14.48	0.518 ^c	117.32 ± 15.49	
Diastolic BP (mmHg)						
T0	79.94 ± 11.59	0.002 ^a	83.29 ± 15.13	0.014 ^a	79.82 ± 10.35	0.001 ^a
T30	74.09 ± 8.57	0.013 ^b	74.88 ± 11.87	< 0.001 ^b	72.53 ± 9.57	0.015 ^b
T60	74.15 ± 7.93	1.0 ^c	72.06 ± 11.39	0.378 ^c	73.15 ± 12.24	1.0 ^c
SpO ₂ (%)						
T0	95.94 ± 1.78	0.024 ^a	95.59 ± 2.50	0.009 ^a	95.41 ± 2.08	0.078 ^a
T30	94.74 ± 2.59	0.932 ^b	94.12 ± 3.09	0.004 ^b	94.35 ± 2.34	0.003 ^b
T60	95.44 ± 2.64	0.209 ^c	94.29 ± 2.41	1.0 ^c	93.82 ± 2.02	0.432 ^c

T0: prior to the initiation of the analgesic infusion. T30: 30 minutes after the analgesic infusion T60: 60 minutes after the analgesic infusion.

Between-group comparison of SpO₂ (one-way ANOVA): T0 $p = 0.584$; T30 $p = 0.635$; T60 $p = 0.018$ (Tukey post hoc: combination vs. dexketoprofen, $p = 0.016$).

^a: comparison between T0 and T30; ^b: comparison between T0 and T60; ^c: comparison between T30 and T60.

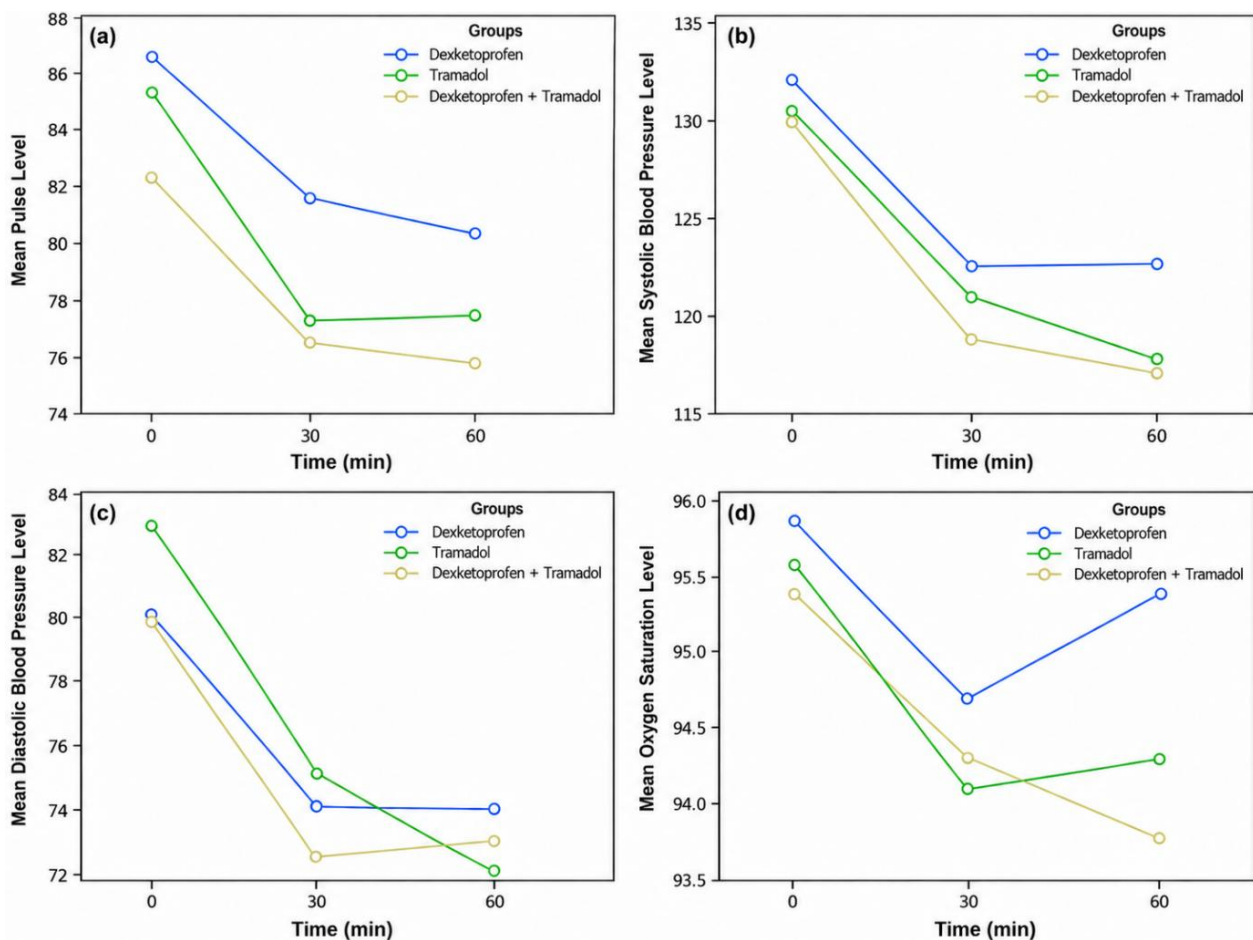


Fig. 2. Changes in vital signs during the observation period: mean values of (a) heart rate; (b) systolic blood pressure; (c) diastolic blood pressure; (d) peripheral oxygen saturation (SpO₂) measured at baseline (T0), 30 minutes (T30), and 60 minutes (T60) following intravenous administration of dexketoprofen trametamol, tramadol, or their combination. Heart rate and blood pressure decreased from T0 to T30 in all groups and remained stable thereafter.

SpO₂ decreased transiently in the dexketoprofen group and remained lower at T60 in the tramadol-containing groups. Because pain scores were not collected, these changes cannot be attributed to analgesic efficacy.

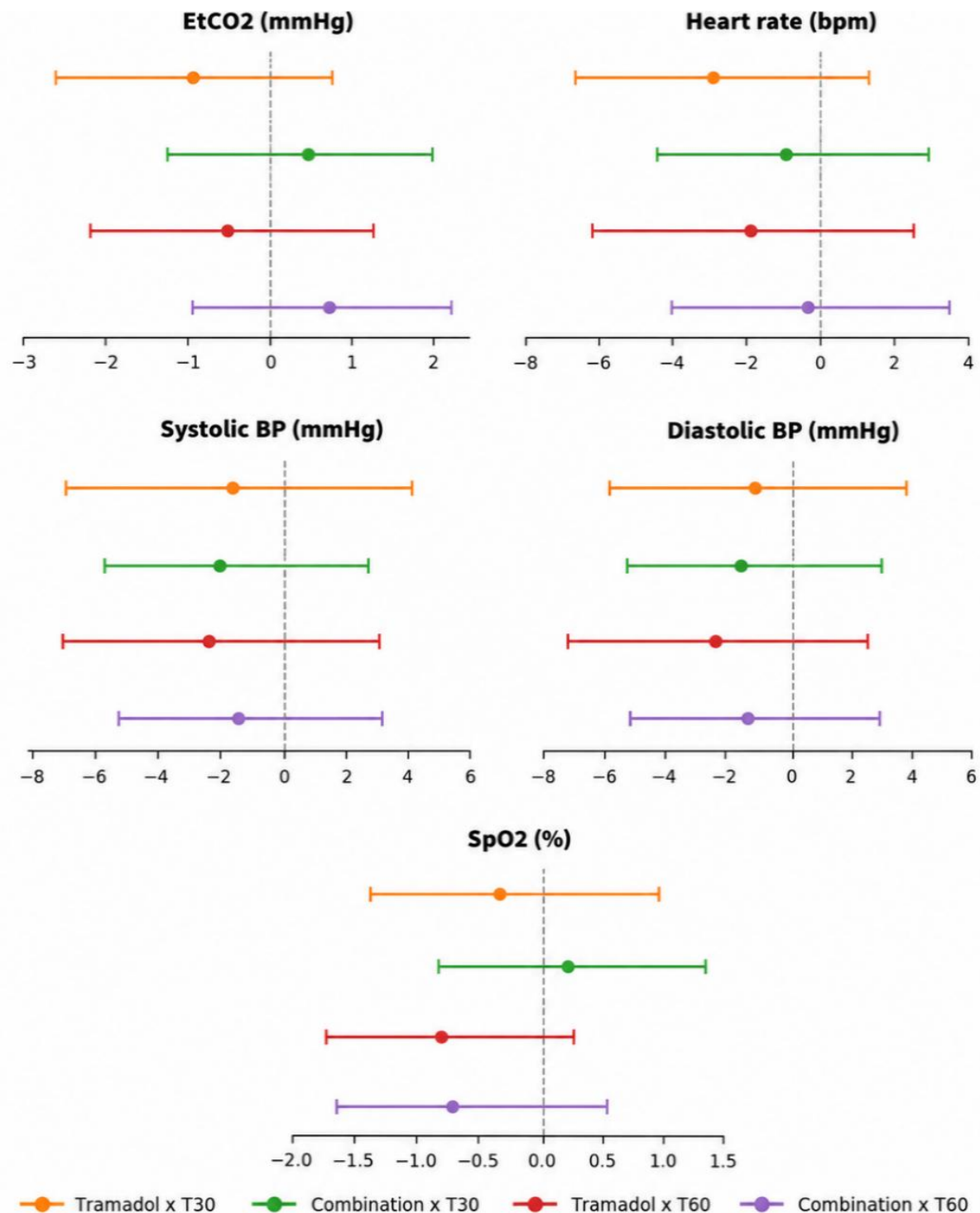


Fig. 3. Linear mixed-effects sensitivity analysis of repeatedly measured parameters. Point estimates and 95% confidence intervals for the group $\times$ time interaction terms (Tramadol $\times$ T30, Combination $\times$ T30, Tramadol $\times$ T60, Combination $\times$ T60, each relative to the dexketoprofen group at T0) are shown for EtCO₂, heart rate, systolic blood pressure, diastolic blood pressure, and SpO₂. All confidence intervals cross zero, indicating no statistically significant interaction between treatment group and time for any parameter.

No significant between-group differences were observed in arterial pH, bicarbonate, PCO₂, lactate, or base deficit at either T0 or T60 (baseline p values: pH 0.227, bicarbonate 0.647, PCO₂ 0.266, lactate 0.722, base deficit 0.472; 60-minute p values: 0.190, 0.099, 0.465, 0.448, and 0.115, respectively). Subsequent within-group analyses revealed a statistically significant decline in lactate levels from T0 to T60 across all three treatment groups (dexketoprofen $p = 0.003$, tramadol $p = 0.008$, combina-

tion $p = 0.001$). Concurrently, base deficit and other blood-gas parameters demonstrated stability (see Table 3 and Fig. 4).

Taken together, these findings indicate that dexketoprofen trometamol, tramadol, and their combination did not adversely affect surrogate markers of global tissue perfusion during the first hour of treatment and were instead associated with a modest, consistent reduction in serum lactate.

Table 3. Comparison of perfusion-related arterial blood-gas parameters between treatment groups.

Variables		Group 1 (n = 34)		Group 2 (n = 34)		Group 3 (n = 34)	
		T0	T60	T0	T60	T0	T60
pH		7.40 ± 0.05	7.40 ± 0.04	7.40 ± 0.04	7.40 ± 0.04	7.38 ± 0.054	7.39 ± 0.03
	p	0.909		0.831		0.630	
HCO ₃ (mEq/L)		24.18 ± 2.6	24.29 ± 2.62	23.54 ± 3.3	24.81 ± 2.71	23.99 ± 2.48	23.52 ± 2.01
	p	0.795		0.102		0.162	
PCO ₂ (mmHg)		39.59 ± 5.79	39.64 ± 4.31	38.45 ± 7.01	40.82 ± 5.64	41.15 ± 7.56	39.49 ± 4.39
	p	0.950		0.117		0.195	
Lactate (mmol/L)		1.89 ± 0.67	1.55 ± 0.60	1.81 ± 0.79	1.48 ± 0.59	1.97 ± 1.05	1.35 ± 0.74
	p	0.003		0.008		0.001	
Base deficit (mEq/L)		0.18 ± 2.28	0.18 ± 2.78	-0.68 ± 3.8	0.56 ± 2.59	-0.38 ± 2.26	-0.68 ± 1.99
	p	1.0		0.110		0.348	

T0: prior to the initiation of the analgesic infusion.

T30: 30 minutes after the analgesic infusion.

T60: 60 minutes after the analgesic infusion.

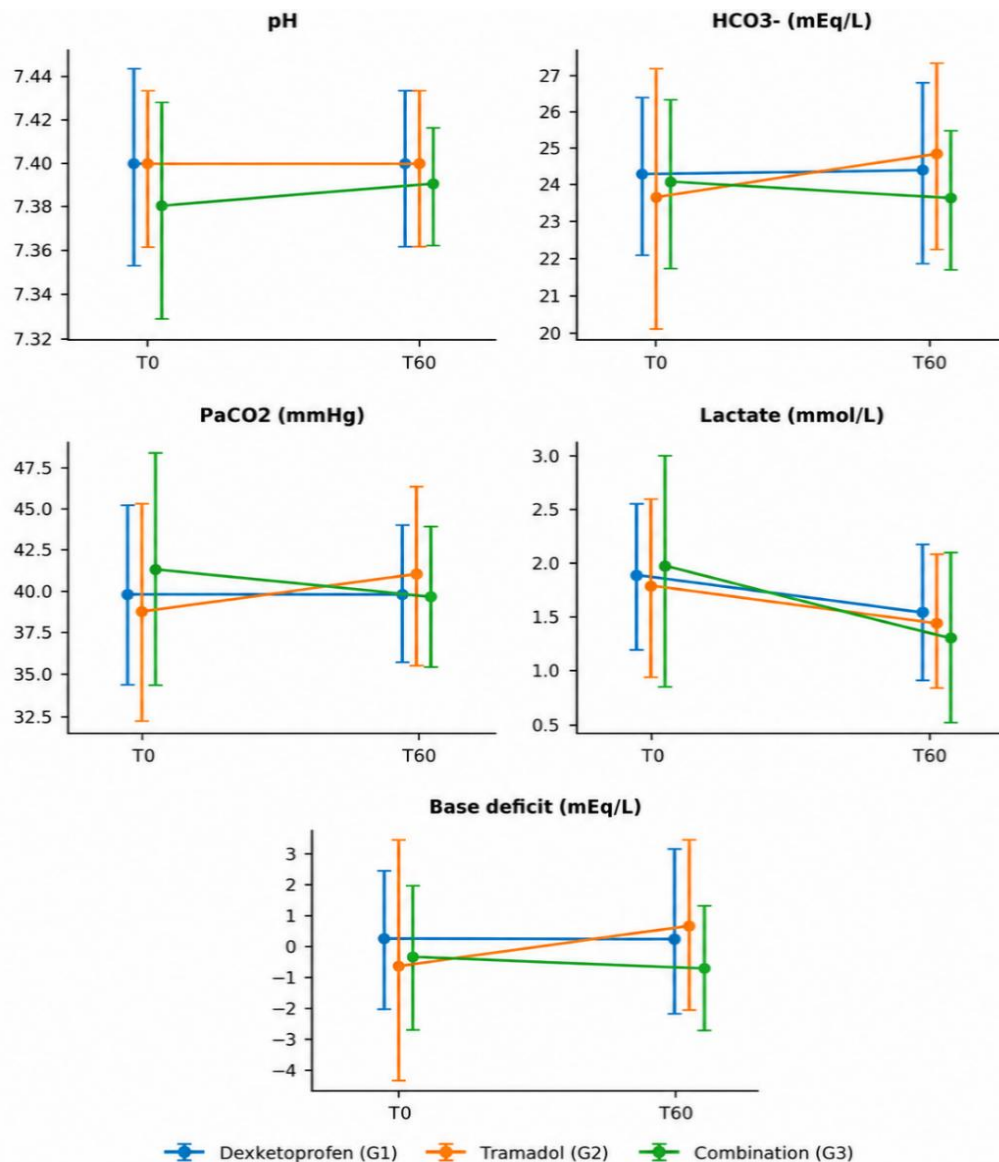


Fig. 4. Arterial blood-gas parameters before and after analgesic treatment; mean values of arterial blood-gas parameters, including pH, bicarbonate (HCO₃⁻), partial pressure of carbon dioxide (PCO₂), serum lactate, and base deficit, measured at baseline (T0) and 60 minutes (T60) following intravenous administration of dexketoprofen tramadol, tramadol, or their combination. Across all treatment groups, arterial blood-gas parameters remained stable over time, with a consistent reduction in serum lactate levels observed at 60 minutes.

4. Discussion

In this prospective randomised study of patients presenting to the emergency department with renal colic, intravenous dexketoprofen trometamol, tramadol, and their combination had comparable short-term effects on EtCO₂, hemodynamic variables, and arterial blood-gas parameters, with no significant group x time interaction for any repeatedly measured parameter. However, SpO₂ exhibited a modest decline that persisted at 60 minutes in the tramadol-containing arms, where all transient desaturations below 90% occurred. Notably, none of these cases necessitated supplemental oxygen or respiratory intervention. It is important to note that the study was not designed or powered to assess comparative safety. Therefore, it is essential that these findings are regarded as physiological observations only.

The clinical relevance of these findings is evidenced by the fact that acute renal colic is characterised not only by severe pain but also by pronounced sympathetic activation. This, in turn, may transiently influence cardiovascular dynamics and metabolic demand. It is therefore reasonable to hypothesise that effective analgesia will attenuate sympathetic tone, which may result in favourable changes in physiological parameters. Conversely, opioid-based analgesia, particularly in higher doses, has the potential to impair ventilation and gas exchange, which raises concerns regarding respiratory safety in spontaneously breathing patients. In the present study, EtCO₂ remained unchanged with all regimens at standard intravenous doses, whereas the modest and sustained SpO₂ decrease in the tramadol-containing arms may reflect a mild opioid-related effect on oxygenation that did not require intervention in this low-risk population.

Numerous studies and meta-analyses have compared the analgesic efficacy and adverse-event profiles of NSAIDs and opioids in renal colic; however, the majority have focused primarily on pain scores, rescue analgesia requirements, and gastrointestinal side effects [6–9,11]. Conversely, data concerning the physiological consequences of analgesic choice, particularly with regard to perfusion-related markers, remain limited. The present study extends the extant literature by demonstrating that commonly used intravenous analgesic regimens for renal colic exert neutral short-term effects on EtCO₂, a parameter increasingly recognised as an indirect marker of cardiac output and tissue perfusion.

Extensive validation of EtCO₂ monitoring has been undertaken in critically ill populations, where low EtCO₂ values are associated with reduced cardiac output, elevated lactate levels, and increased mortality in conditions such as shock, sepsis and cardiac arrest [14,19–22]. In such contexts, EtCO₂ serves as a dynamic, non-invasive indicator of systemic perfusion and response to resuscitative interventions. Nevertheless, the clinical applicability of EtCO₂ for detecting more subtle physiological changes in stable emergency department patients remains to be firmly established. The present findings suggest that, in patients with isolated acute pain and preserved hemodynamic stability, alterations in perfusion induced by analgesia may be too modest to elicit measurable changes in EtCO₂.

It is noteworthy that, despite the stability of EtCO₂ and other vital parameters, a statistically significant reduction in serum lactate levels was observed across all treatment groups. This consistent finding is likely indicative of a reduction in metabolic stress induced by pain, as opposed to a direct effect of the analgesics on systemic perfusion. As serial pain scores and treatment-response data were not collected in this study, it is important to regard this explanation as a hypothesis rather than a demonstrated mechanism linking analgesia to lactate clearance. It is well established that acute pain increases catecholamine release, glycolytic flux, and lactate production, even in the absence of overt hypoperfusion. It may therefore be hypothesized that effective pain control contributes to the normalization of metabolic homeostasis, reflected in modest lactate clearance, although this study cannot establish this mechanism directly. Given that baseline lactate values in this cohort were largely within normal or near-normal ranges, the observed reductions should be interpreted as markers of stress resolution rather than indicators of recovery from pathological hypoperfusion.

Tramadol is frequently regarded as a comparatively safer opioid with respect to respiratory depression due to its weak μ -opioid receptor agonism and additional monoaminergic mechanisms. As demonstrated in previous clinical studies comparing tramadol with morphine by the intravenous and epidural routes and in pharmacovigilance data, clinically significant respiratory depression with tramadol is rare at therapeutic doses [23–25]. Consistent with this, no participant in the present study required respiratory intervention; however, the sustained SpO₂ decrease observed in the tramadol-containing arms indicates that monitoring remains warranted, as discussed below.

While the absence of between-group differences may initially appear to be a null finding, in the context of ED analgesic safety, it carries direct practical value. In clinical practice, tramadol is frequently avoided or underdosed because of concerns about respiratory depression, even at doses well within the recommended limits. In the present study, intravenous tramadol—either as an isolated treatment or in combination with dexketoprofen trometamol—did not alter EtCO₂ during the first hour of treatment in non-intubated, hemodynamically stable renal colic patients. However, SpO₂ decreased modestly and remained lower at 60 minutes in the tramadol-containing arms, in which all seven transient desaturations below 90% occurred. This data therefore provide reassurance regarding hypercapnic ventilatory depression but not regarding oxygenation, and, given the absence of a dedicated safety or non-inferiority design, they cannot be interpreted as a formal demonstration of comparative safety. These findings also suggest that capnography and pulse oximetry provide complementary rather than interchangeable information when tramadol is administered to spontaneously breathing patients.

From a pragmatic standpoint, these findings suggest that, in hemodynamically stable patients with renal colic, the choice between NSAID-based, tramadol-based, or combination analgesic strategies is unlikely to influence short-term global perfusion as assessed by EtCO₂ and arterial blood-gas analysis. Tramadol, at the doses admin-

istered in this study, did not alter EtCO₂; however, given the SpO₂ decrease observed in the tramadol-containing arms, its use should be accompanied by standard monitoring and adherence to dosing limits, particularly in patients with risk factors for respiratory depression [24,25]. Beyond these considerations, the selection of analgesics may be more appropriately guided by contraindications, anticipated side-effect profiles, prior analgesic exposure, and individual patient characteristics, in line with current guideline recommendations [3,10]. It can be hypothesized that lactate may be a more responsive short-term metabolic marker than EtCO₂ in this relatively low-risk population, although its relationship with pain relief could not be assessed in this study.

Nevertheless, caution is warranted when extrapolating these results to patients with hemodynamic instability, significant cardiopulmonary comorbidities, or those requiring repeated or higher-dose opioid administration. In such populations, significant disparities may be observed in both perfusion dynamics and respiratory risk profiles, thus rendering EtCO₂ monitoring a potentially more significant clinical tool.

4.1. Limitations

A significant strength of this study is its prospective, randomized, three-arm design, which facilitates direct comparison of NSAID, opioid, and combination analgesia using objective hemodynamic and metabolic endpoints. Serial EtCO₂ and blood-gas measurements further characterize the immediate physiological response to analgesia in a real-world emergency department setting.

It is imperative to acknowledge the limitations of the present study. Firstly, this was a single-center study with a modest sample size and only 60 minutes of follow-up, so delayed or cumulative effects could not be assessed. Secondly, the distribution of sex differed between groups, with a higher proportion of male subjects in the combination arm. However, there is no clear biological rationale to predict sex-specific differences in short-term EtCO₂ responses to these drugs. Thirdly, the pain scores and clinical outcomes (e.g., the use of rescue analgesia or the time to disposition) were not systematically reported, thus limiting the direct linkage between perfusion markers and analgesic efficacy. It is important to note that EtCO₂ and lactate are global indices that may not detect subtle regional or microcirculatory perfusion abnormalities that do not substantially alter overall CO₂ elimination or lactate production [20–22].

Further research with larger, more heterogeneous populations, longer follow-up, and combined assessment of pain scores, microcirculatory indices, and clinical outcomes could assist in clarifying whether specific analgesic choices offer any nuanced hemodynamic advantages in acute renal colic.

5. Conclusions

In hemodynamically stable adults presenting to the emergency department with renal colic, intravenous dextetoprofen trometamol, tramadol, and their combination had similar short-term effects on EtCO₂, hemody-

namic variables, and arterial blood-gas parameters. EtCO₂ remained unchanged with all regimens, whereas SpO₂ decreased modestly and remained lower at 60 minutes in the tramadol-containing arms, in which all transient desaturations occurred; capnography and pulse oximetry should therefore be used together when tramadol is administered. The observed reduction in lactate levels across all groups may reflect attenuation of pain-related stress, but this remains hypothetical because pain scores were not collected. Within the limits of a study not designed to assess comparative safety, these findings suggest that the selection of analgesic treatment may be guided by efficacy and patient-specific factors rather than by concerns over short-term perfusion impairment.

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Conflict of Interest

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, DeepL Translate / Write was used exclusively for language editing and stylistic refinement. The authors take full responsibility for the content, interpretation, and conclusions of the published article.

Ethics Approval and Consent to Participate

This study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Approval Number: 2024-16/01; Date: 07 Nov 2024). The first participant was enrolled on 10 November 2024. Written informed consent was obtained from all participants. All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

Gülbahar Demir: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing.

Mevlana Gül: investigation, methodology, writing – original draft, writing – review & editing.

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