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ORIGINAL RESEARCH

Superior efficacy of intramuscular diclofenac compared to intravenous tramadol for acute renal colic in northern Thai patients: A randomised double-blind, sham-controlled trial

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Abstract

Objective: The present study aimed to compare time to effective pain relief between diclofenac 75 mg intramuscular (IM) and tramadol 50 mg intravenous (IV) for ED patients with acute renal colic.

Methods: A randomised, double-blinded, sham-controlled, superiority trial was conducted. Patients diagnosed with acute renal colic (hydronephrosis and/or stone visualisation on point-of-care ultrasound) in the ED were randomly assigned to receive an IM injection of 75 mg of diclofenac or IV tramadol 50 mg. Pain relief was defined as a numerical rating scale reduction of two or more points (standard 0–10 scale) and a reduction of at least one level of pain transition question ('much better', 'little better', 'unchanged', 'little worse', 'much worse'). The primary outcome was the multivariable-adjusted subdistribution-hazard ratio (SHRs) within 120 min in the ED, estimated using the cumulative incidence function (CIF). The secondary outcome compared the average time to pain relief using the restricted mean survival time (RMST).

Results: A total of 68 patients were randomised, with 34 patients allocated to each group. At the 120 min, pain relief was reported in diclofenac and tramadol, 32 (94%) and 22 (65%) patients respectively. SHR was 2.86 (95% CI: 1.80–4.55; *P* value <0.001). For diclofenac and tramadol, the RMSTs were 37.09 min (95% CI: 30.00, 44.15) and 78.74 min (95% CI: 66.49, 90.99) respectively, with the difference of 41.67 min (95% CI: 55.71, 27.62).

Conclusion: Diclofenac 75 mg IM provides faster effective pain relief compared with tramadol 50 mg IV.

Key findings

- Intramuscular administration of diclofenac resulted in a more rapid alleviation of pain in individuals experiencing acute renal colic and may potentially lead to shorter stays within the ED.
- The intravenous tramadol was associated with a higher incidence of nausea vomiting.
- Intramuscular diclofenac demonstrated a less incidence of patient requiring rescue analgesia.

Key words: *diclofenac, randomised controlled trial, renal colic, tramadol.*

Introduction

Acute renal colic is a severe form of sudden flank pain caused by the obstruction of the urinary tract by a calculus, often accompanied by nausea and vomiting. The pain results from a combination of ureteral muscle spasms, increased proximal ureteral dilation and peristalsis, which stimulate submucosal stretch receptors in the ureter, renal pelvis and capsule.[1] Appropriate clinical evaluation with prioritising rapid pain relief is crucial for effective acute management.[2]

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as

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the first-line agents[3,4] for pain relief because of their direct action on the cause of pain.[5] Many studies have demonstrated that a 75 mg dose of diclofenac is effective in reducing pain.[6,7] Because of diclofenac's poor solubility and its potential risk of venous thrombosis, the Medical Council of Thailand has limited use of the IV bolus and instead recommends administering 75 mg of diclofenac intramuscularly (IM).[8] However, despite its quick onset and ease of administration, there are disadvantages, including unpredictable absorption, delayed onset and risks of complications such as sciatic nerve injury.[9] In Thailand, according to the Announcement of Medical and Nursing Council of Thailand, diclofenac IM can only be administered by doctors because of safety concerns.[10]

On the other hand, opioid treatment has advantages in terms of treatability, potency, and affordability. Intravenous (IV) tramadol at a dose of 50 mg, a synthetic opioid, is commonly administered[11] because of its lesser effects on respiratory and cardiovascular systems, as well as its low potential for drug abuse[12–14] and the rapid onset of pain relief provided by the IV route. Therefore, in many situations within our setting, clinicians may prefer IV tramadol over intramuscular diclofenac.

Previous studies have demonstrated similar rate of patient with effective pain relief at 30 min post-administration,[6,7] However, the time required to achieve effective pain relief has not been specifically examined. Although the proportion of patients experiencing pain relief may be similar, the exact time to achieve pain relief could vary within the period. Faster pain relief has the potential to improve both the patient experience and enhance the efficiency of ED patient flow. The primary aim of the present study is to compare the time to pain relief between diclofenac 75 mg IM and tramadol 50 mg IV in patients with acute renal or ureteric colic. The secondary objective is to compare the average time to pain relief, the number of patients needing rescue analgesia and the incidence of adverse events associated with both drugs.

Methods

Study design and setting

The present study was a randomised, double-blinded, sham-controlled, superiority trial conducted in the Emergency Department of Lampang Hospital, Thailand, from April 2022 to March 2023 The study protocol was registered at https://clinicaltrials.gov/ (NCT06231043). The Institutional Review Board (IRB) of Lampang Hospital approved the study protocol (CERT No. 100/66) on 27 April 2022. The reporting of the present study adhered to the CONSORT guidelines.[15]

Participants and data collection

Patients presenting to the ED with acute renal colic or ureteric colic during the study period were included. Confirmation of acute renal colic or ureteric colic was performed using renal point-of-care ultrasound (POCUS) by emergency specialist doctors before randomisation. The diagnostic criteria included pyeloureteral dilatation and/or direct visualisation of stones.[16–18] Inclusion criteria were individuals aged 18 years or older with a pain scale score of ≥4 on the Numeric Rating Scale (NRS). Exclusion criteria included pregnancy or lactation, contraindications to tramadol or diclofenac, prior receipt IV or IM analgesia within the past 4 h, urinary tract infection, infection at the injection site, bilateral severe hydronephrosis, acute renal failure or chronic kidney disease up to stage III, and patients unable to provide informed consent. Baseline data on age, sex, BMI, degree of hydronephrosis,[19] and duration of pain prior to the visit were collected.

Randomisation

All patients included in the study were randomly assigned to one of two arms in a 1:1 ratio. The randomised sequence was conducted using a computer-generated block of 4, performed by an independent researcher. The sequences for randomisation were stratified based on sex and the level of pain (categorised as pain scale 4–6 or 7–10 on the NRS). The intervention code in the randomised sequence was accessible only to the personnel responsible for preparing the interventions, who were not involved in patient recruitment or outcome assessment. Sequentially numbered opaque sealed envelopes (SNOSE) were utilised to conceal the randomisation sequences. These envelopes were opened immediately after patients were enrolled in the study, and all baseline data were collected.

Intervention and blinding

Patients assigned to the diclofenac arm received an intramuscular injection of 75 mg (3 mL) of diclofenac along with an IV infusion of 20 mL of normal saline (sham).[4,8] In the tramadol arm, patients received an intramuscular injection of 3 mL of normal saline (sham), with an IV infusion of 50 mg of tramadol diluted in 20 mL of normal saline[11,13] (Fig. 1). The interventions were prepared and administered by ED healthcare personnel who were not involved in assessing the outcomes. Patients, primary physicians, data collectors, and outcome assessors were all blinded to the treatment assignments.

Efficacy and safety

The primary outcome was the time to pain relief within 120 min. Pain relief was defined as a decrease of at least 2 points on the NRS (ranges from 0 to 10) and an improvement of at least 1 level on a transitional question regarding pain[20,21] (see in Fig. S1). A transition question asked patients to rate their perceived change between two moments in time, with response options such as 'much better', 'a little better', 'unchanged', 'a little worse' and 'much worse'. A change of one level indicates a shift from 'no change' to either 'a little better' or 'a little worse'.[21]

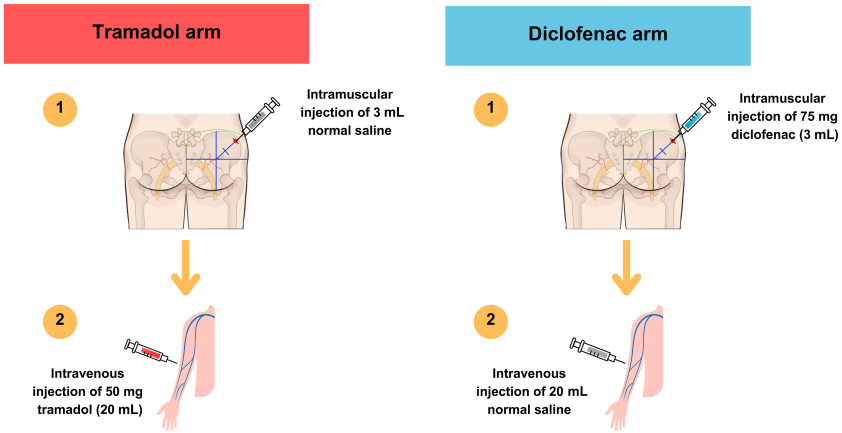

Figure 1. *Intervention procedure.*

Patients who did not achieve pain relief within the 2 h period were considered censored. The rescue analgesia protocol was activated when there was either no reduction in pain within 120 min or when the patient could not tolerate the pain and requested rescue analgesia, (IV morphine 0.1 mg/kg). Patients could request the rescue analgesia at any time during the trial. The pain was assessed every 30 min or until the moment patient reported pain relief or requested rescue analgesia. The secondary outcomes included the average time to pain relief, the number of patients needing rescue analgesia within 120 min in the ED, and the occurrence of adverse events such as nausea, vomiting, allergic reactions, skin infections, and sciatic nerve injury within 120 min in the ED and up to 14 days after discharge. Patients were followed up via telephone on day 3 and day 14 post-treatment to check for any adverse events. There was no drug restriction protocol once patients were discharged from the ED. Both primary and secondary outcomes were assessed by non-researcher medical personnel who were blinded to the treatment assignments.

Statistical analysis

Based on our preliminary analysis, the anticipated hazard ratio was set at 2.0. We assumed consistent enrolment throughout the 2 h period. To ensure a statistical power of 80% at a 5% one-sided significance level using the log-rank test, and considering an anticipated dropout rate of 10%, a total of 66 patients were required.

All statistical analyses were conducted using Stata 17 (StataCorp, College Station, TX, USA). Categorical data were reported with frequency and percentage. Mean and standard deviation (SD) were used to describe normally distributed numerical data, and median and IQR for non-normally distributed numerical data. The normality of data was justified based on the histogram and Shapiro–Wilk test. Standardised difference was used to determine the imbalance baseline factors. Standardised difference more than 10% indicated the potential imbalance of baseline factors between treatment arms.

For the analysis of time to event, patient who experienced acute adverse event (nausea vomiting and allergic reaction) and received rescue analgesia were defined as competing event. Therefore, the Kaplan–Meier method was not appropriate for estimating survival curves for pain relief events. Instead, we utilised the cumulative incidence function (CIF) to illustrate the cumulative incidence curve. The CIF demonstrated the probability of experiencing pain relief by the time t when the patients could also experience adverse event or need rescue analgesia before their pain was relieved within 120 min of the study duration. Subdistribution-hazard ratios (SHRs) and their corresponding 95% confidence intervals (CI) were calculated using a competing risk regression.[22] Multivariable analysis was employed and adjusted for imbalance baseline factors to minimise bias and enhance study power.[23] Proportional subhazards assumption was evaluated based on cumulative sums of residuals test.[24]

For the secondary outcome, the average time to pain relief and the differences between both interventions at 120 min was estimated using the restricted mean survival time (RMST), which does not rely on the proportional hazard assumption.[25] Estimations at these additional time points (30 and 60 min), rather than just at 120 min, aimed to demonstrate the dynamics of patients experiencing rapid responses and other response patterns in both treatment groups. The cumulative number of patients requesting rescue analgesia (failure), along with the absolute risk difference and the incidence of adverse events between the two treatment arms were compared using Fisher's exact probability test, with P-values less than 0.05 considered statistically significant. The analyses were conducted based on the intention-to-treat principle.

Results

Baseline characteristic

A total of 128 patients were initially screened for eligibility. Sixty patients were excluded, as illustrated in Figure 2. The remaining 68 patients were then randomised, with 34 patients allocated to the diclofenac arm and 34 patients to the tramadol arm. The majority of patients in both arms were male, accounting for 58.8% in the diclofenac arm and 61.8% in the tramadol arm. Over one-third of the patients had a history of previous renal colic. Additionally, around 65% of all patients showed a mild degree of hydronephrosis.

There were potential imbalances in baseline factors between the two arms, including mean age, history of renal or ureteric colic, characteristics of renal stones, baseline pain score and duration of pain prior to the visit (see Table 1). No statistically

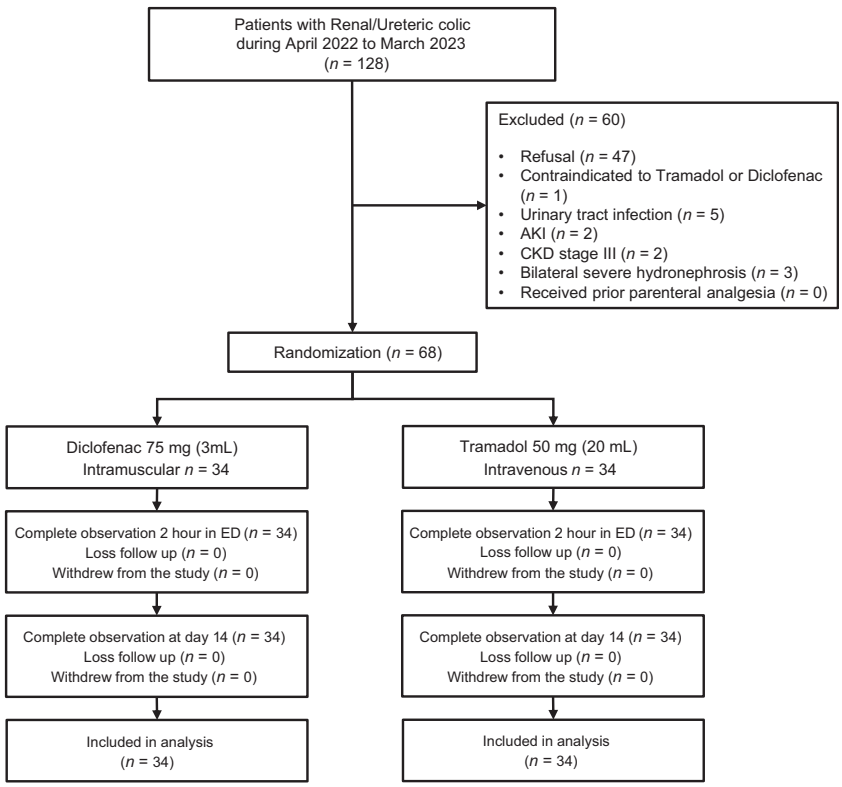

Figure 2. *Study flow diagram. AKI, acute kidney injury; CKD, chronic kidney disease.*

TABLE 1. *Baseline clinical characteristic*

Baseline factor	Diclofenac group $n = 34$, n (%)	Tramadol group $n = 34$, n (%)	Std diff (%)
Male	20 (58.8)	21 (61.8)	5.9
Age (year), mean ± SD	50.0 ± 12.6	53.5 ± 13.0	27.7
Body mass index (kg/m^2), mean ± SD	24.5 ± 4.1	24.1 ± 3.6	−9.8
History of renal/ureteric colic	12 (35.3)	14 (41.2)	11.9
Degree of hydronephrosis			
No hydronephrosis	5 (14.7)	5 (14.7)	0
Mild	22 (64.7)	22 (64.7)	
Moderate	6 (17.7)	6 (17.7)	
Severe	1 (2.9)	1 (2.9)	
Characteristics of renal stone			
Multiple renal stones	22 (64.7)	24 (70.6)	−12.4
Few renal stones	12 (35.3)	10 (29.4)	
Duration of pain prior visiting ED (h), median (IQR)	4 (2, 8)	4 (2, 6)	16.5
Pain score at ED, mean ± SD	7.6 ± 1.9	7.9 ± 1.8	17.3

SD, standard deviation; Std diff, standardised difference.

significant differences were found in the remaining baseline factors.

Treatment efficacy and safety

There were no exclusions or losses among patients from the study after randomisation, up to 14 days post-treatment (Fig. 2). At the 120 min post-treatment, pain relief was observed in 32 patients (94.1%) in the diclofenac arm and 22 patients (64.7%) in the tramadol arm. Figure 3 illustrates the cumulative incidence function curve of diclofenac and tramadol. The multivariable SHR was 2.86 (95% CI: 1.80–4.55; P value <0.001).

Table 2 compares the proportion of patients who achieved pain relief, the RMST and the difference in RMST at each time point. Diclofenac IM demonstrated a more rapid average time to pain relief (RMST) at every time point. At 30 min, the RMSTs for patients in the diclofenac and tramadol arms were 24.87 min (95% CI: 22.57, 27.18) and 28.19 min (95% CI: 26.68, 29.70), respectively. At 120 min, the RMSTs were 37.09 min (95% CI: 30.00, 44.15) for the diclofenac arm and 78.74 min (95% CI: 66.49, 90.99) for the tramadol arm. The difference in RMST between the two arms increased over time, with differences of approximately 3, 16 and 41 min at 30, 60 and 120 min post-treatment, respectively. Additionally, the change in average time to pain relief between 30 and 120 min was smaller in the diclofenac arm compared to the tramadol group (approximately 12 min for diclofenac IM *vs* approximately 50 min for tramadol IV). Further details on other time points are provided in Table 2.

Table 3 compares the cumulative failure proportion and demonstrates the absolute risk difference at each time point between both treatments. During the 2 h period in the ED, 2 patients assigned to the diclofenac group requested additional analgesia, whereas 12 patients in the tramadol group did so. Notably, half of the patients who failed to achieve pain relief in the tramadol group requested additional analgesia within the first 30 min. There was a

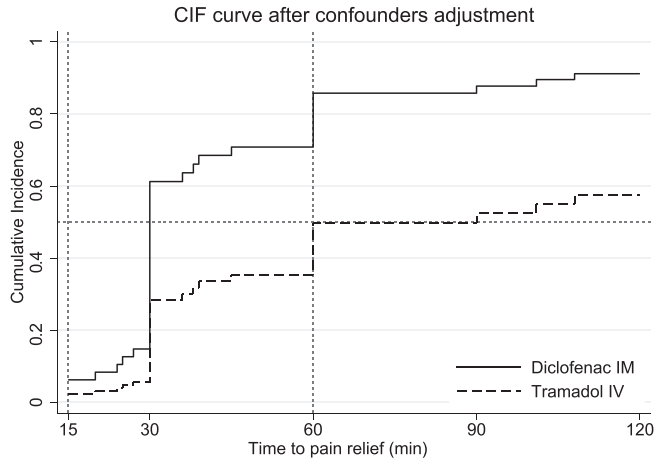

Figure 3. *Cumulative incidence function curve of diclofenac and tramadol. IM, intramuscular; IV, intravenous.*

statistically significant cumulative absolute risk difference between both arms, favouring the diclofenac arm. The differences showed an increasing trend over time, from −17.6% (95% CI: −30.5, −4.8) at 30 min to −29.4% at 120 min (95% CI: −47.3, −11.5) (Table 3).

The incidence of patients requiring rescue analgesia was 5.9% in the diclofenac arm compared to 35.2% in the tramadol arm ($P = 0.003$). During the 120 min post-treatment period, there were no serious adverse event in both arms. Two patients (5.9%) in the tramadol arm experienced nausea and vomiting, whereas no adverse events were reported in the diclofenac arm ($P = 0.493$). There were no allergic reactions, skin infections or sciatic nerve injuries reported throughout the study duration (14 day post-treatment).

Discussion

In the present study, we compared the effectiveness in terms of time to pain relief and safety of diclofenac and tramadol for treating renal or ureteric colic. Our results showed that diclofenac provided faster pain relief compared to tramadol in patients during 120 min post-treatment period with an SHR of 2.86 (95% CI: 1.80, 4.55).

Substantial studies have compared pain relief between NSAIDs and opioids at different time points.[26–30] Previous evidence showed a higher rate of complete pain relief in patients treated with NSAIDs at 30 min, although the pooled result lacked statistical significance in the meta-analysis.[8] Diclofenac IM provided a higher proportion (79.4%) of pain relief compared to tramadol IV, where only 32.4% of patients achieved pain relief at this time point. Our study's results align with the conclusions of Salameh et al.[26] However, there was a significant difference in the proportion of patients achieving pain relief with tramadol (32.4% in our study *vs* 61% in Salameh's study). The lower dose of tramadol in our study (50 mg *vs* 100 mg in Salameh's) may have played a key role. Another potential explanation could be differences in baseline characteristics, such as age (approximately 50 years old in our study *vs* 37 years old in Salameh's) and gender distribution. Evidence indicates that many molecular and cellular events critical to opioid analgesia and tolerance are age-dependent,[31] and the difference of opioid receptor function between sexes may also contribute.[32,33]

Despite, at 30 min, the patient in the diclofenac arm achieved pain relief slightly sooner, approximately 3 min. However, the patients included to estimate the average time to pain relief in the tramadol group represented only one-third of the

TABLE 2. *The restricted mean survival time differences (min) between diclofenac and tramadol at 30, 60 and 120 min*

Time	Pain relief (%) Diclofenac arm Total $n = 34$ (95% CI)	Pain relief (%) Tramadol arm Total $n = 34$ (95% CI)	Adjusted RMST† diclofenac arm (95% CI)	Adjusted RMST† tramadol arm (95% CI)	Adjusted RMST† difference (95% CI)
30 min	27 (79.4) (62.1–91.3)	11 (32.4) (17.4–50.5)	24.87 (22.57, 27.18)	28.19 (26.68, 29.70)	−3.32 (−6.10, −0.54)
60 min	32 (94.1) (80.3–99.3)	19 (55.9) (37.9–72.8)	34.65 (29.25, 40.05)	50.73 (45.91, 55.54)	−16.07 (−23.21, −8.94)
120 min	32 (94.1) (80.3–99.3)	22 (64.7) (46.4–80.3)	37.09 (30.00, 44.15)	78.74 (66.49, 90.99)	−41.67 (−55.71, −27.62)

†Adjusted for age, history of renal/ureteric colic, characteristics of renal stone, duration of pain prior visiting ED, pain score at ED. CI, confidence interval; RMST, restricted mean survival time.

TABLE 3. *Cumulative failure proportion and absolute risk reduction between diclofenac and tramadol at 30, 60, 90 and 120 min after receiving intervention*

Time point	Failure (%) Diclofenac arm Total $n = 34$	Failure (%) Tramadol arm Total $n = 34$	Cumulative absolute risk difference (95% CI)	*P*-value
30 min	0 (0)	6 (17.6)	−17.6% (−30.5, −4.8)	0.008
60 min	1 (2.9)	8 (23.5)	−20.6% (−35.9, −5.2)	0.003
90 min	2 (5.9)	9 (26.4)	−20.6% (−37.4, −3.8)	0.009
120 min	2 (5.9)	12 (35.3)	−29.4% (−47.3, −11.5)	<0.001

CI, confidence interval.

total, possibly indicating only fast responders. The difference in time to pain relief became more pronounced over the observed period. The analysis using the RMST approach offers valuable insights into the clinical effectiveness of diclofenac and tramadol by highlighting the time required for clinically significant improvement. At 120 min, when the majority of patients in both treatment groups achieved pain relief, tramadol IV showed a delayed response with slightly higher variation in patient response. The present study revealed findings against the concern about the delayed onset and unpredictable absorption of the diclofenac IM route.

In the tramadol arm, only two patients (5.9%) experienced nausea and vomiting. The incidence of adverse events in our study was slightly higher compared to a previous study (4.2%), which compared subcutaneous (SC) tramadol with intramuscular (IM) ketorolac.[27] This discrepancy could be because of the older age of patients in our study or the difference in the route of administration. Despite tramadol being a weaker opioid, opioid-induced nausea and vomiting (OINV) remains common, particularly when administered parenterally.[12]

Our study addresses both the efficacy and common concerns regarding the use of diclofenac IM and tramadol IV in treating acute renal colic in resource-limited settings. Although our study supports that diclofenac use over tramadol may not be novel, demonstrating the shorter time to effective pain relief adds weight to the existing evidence. Additionally, the lower percentage of patients needing rescue analgesia and fewer adverse events suggest the potential benefit of using diclofenac IM in reducing ED stay times. However, this additional benefit would require a specific study to confirm. In our context, the findings may raise clinician awareness of the benefits of diclofenac and allay pre-existing concerns around its use.

Limitation

First, the sample size of our study might be relatively small compared to previous studies. However, we performed a post hoc power analysis based on an SHR of 2.86 and 68 patients using a two-sided test. The post hoc power calculation was 96.5%. Given the magnitude of the SHRs, it seems reasonable to suggest that diclofenac could significantly lead to quicker pain relief compared to tramadol. Second, we employed a sham method to maintain blinding. However, the difference between the intervention and the sham might be the sensation during injection because of differences in viscosity. The likelihood of patients discerning which one was the intervention based on their experience and recall capacity is minimal. Third, we did not collect patient satisfaction regarding the injection site. This type of information could also impact the decision to choose the first-line drug for each individual. Last, it is important to note that the present study was conducted in a single tertiary care centre's ED. Therefore, the findings of our study may not be applicable to other clinical settings.

Conclusion

For ED patients with acute renal colic, IM diclofenac provided faster effective pain relief with reduced need for rescue medication compared with IV tramadol. In the absence of contraindications, the findings support the use of diclofenac over tramadol.

Acknowledgements

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Author contributions

JY: Conceptualisation, formal analysis, methodology, investigation, writing – original draft. WK: Supervision, methodology, conceptualisation, data curation. TL: Supervision, methodology, conceptualisation. JP: Supervision, methodology, formal analysis. SL: Supervision, methodology, formal analysis. NU: Investigation, data curation, visualisation. PW: Writing – review & editing, conceptualisation, formal analysis, methodology, supervision, visualisation.

Competing interests

None declared.

Ethics approval and consent to participate

The study protocol was registered at https://clinicaltrials.gov/ (NCT06231043).

The Institutional Review Board (IRB) Lampang Hospital approved the study protocol (CERT No. 100/66). All patients provided written informed consent prior to study inclusion and randomisation. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

None of the individual person's data was used in the present study.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Figure S1. Anchor-based methods for assessing pain relief. The top section illustrates a numeric rating scale (0–10), where a reduction of pain by ≥2 points (red arrow) is considered minimal clinically importance difference (MCID). The bottom section represents transition questions assessing changes in pain perception, ranging from 'Very much worse' to 'Much better'. A shift of one level (red arrow) is MCID. Patients are considered to have achieved pain relief when they exceed the MCID thresholds for both the numeric rating scale and the transition questions.