Randomised Controlled Trial

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Efficacy and safety of ketorolac and dexamethasone for preventing renal colic post stent removal: a randomized triple-blind, placebo-controlled clinical trial

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Background: Renal colic following stent removal post-ureteroscopy is a significant clinical issue. This study aims to evaluate the efficacy and safety of intramuscular ketorolac and dexamethasone in preventing renal colic after stent removal.

Methods: A randomized, triple-blind, placebo-controlled clinical trial was conducted with 147 patients. Participants were allocated to three groups: ketorolac only, ketorolac plus dexamethasone, and placebo. The primary outcome was the visual analog scale (VAS) score for pain, assessed at 1- and 7-days post-stent removal. Secondary outcomes included opioid use, emergency department visits, renal colic symptoms, and missed workdays.

Results: The combination group (ketorolac and dexamethasone) demonstrated significantly lower VAS scores at 24 hours compared to the placebo group (2.95 vs. 4.30, $P = 0.008$). Additionally, this group had fewer emergency department visits (2.0% vs. 22.4%, $P = 0.010$) and lower incidences of subjective renal colic (2.0% vs. 20.4%, $P = 0.017$). No significant differences were observed at 7 days post-stent removal.

Conclusion: Intramuscular ketorolac and dexamethasone significantly reduce pain and related complications following stent removal, providing an effective alternative to opioid analgesics.

Keywords: dexamethasone, ketorolac, pain management, renal colic, stent removal

Introduction

Renal colic following stent removal post-ureteroscopy is a significant clinical issue, characterized by severe flank pain due to ureteral spasm or obstruction[1,2]. Although the pain associated with acute stone passage is well-documented, the discomfort resulting from the surgical treatment of stones has received less attention.

HIGHLIGHTS

- Renal colic following stent removal post-ureteroscopy is a significant clinical issue.
- Ketorolac plus dexamethasone leads to fewer emergency department visits and incidences of renal colic symptoms.
- Intramuscular ketorolac and dexamethasone offer an effective, opioid-sparing alternative for managing pain following stent removal.

The underlying mechanisms include ureteral edema, inflammation, and ureteral muscle spasms triggered by the stent removal process[3]. Effective strategies to prevent renal colic can significantly enhance patient outcomes and alleviate the burden on healthcare systems.

Ketorolac and dexamethasone were chosen for their potential to mitigate renal colic pain due to their distinct mechanisms of action and previous empirical support. Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), exerts its effect by inhibiting cyclooxygenase enzymes, thereby reducing the synthesis of prostaglandins, which are mediators of inflammation and pain[4]. This property makes ketorolac a potent analgesic for acute pain management, including renal colic. Prior studies have demonstrated the efficacy of ketorolac in managing acute pain in various clinical scenarios, reinforcing its potential utility in preventing renal colic post-stent removal[1,2,4,5].

Dexamethasone, a corticosteroid, works by suppressing inflammation through the inhibition of multiple inflammatory pathways, including the suppression of cytokine production and inhibition of

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phospholipase A2 activity, which reduces arachidonic acid release-[6]. This leads to a decrease in the formation of pro-inflammatory mediators. Dexamethasone's anti-inflammatory effects are well-documented in various medical conditions, and its use in managing pain associated with inflammation has been validated in several studies[6,7]. Given these properties, dexamethasone could effectively reduce the inflammatory response and subsequent pain following stent removal, thus addressing one of the primary causes of renal colic.

In this study, we aim to evaluate the efficacy and safety of intramuscular ketorolac and dexamethasone in preventing renal colic after stent removal. Previous research, such as the study by Johnson et al., demonstrated that ketorolac alone reduced unplanned emergency department or clinic visits due to renal colic, though it did not significantly lower overall pain scores[3]. Our study will assess the possible synergistic clinical effects of adjunctive ketorolac and dexamethasone, aiming to enhance the preventative impact on renal colic post-stent removal.

Methods

Study design

This study was a randomized, triple-blind, and placebo-controlled clinical trial that was performed on patients referred to the Urology clinic between March and May 2024 to assess the effects of intramuscular ketorolac and dexamethasone for stent removal pain. The protocol of the trial was approved by the Ethics Committee and the study was performed in accordance with the Declaration of Helsinki and its subsequent revisions. Informed consent was obtained from all participants prior to inclusion.

Study participants and procedures

This study was performed on adult patients that underwent stent placement for renal/ureteral stones. After stent placement, patients were discharged with standard discharge medications, including acetaminophen, tamsulosin (until 3 days after stent removal), phenazopyridine, and diclofenac. Antibiotics were only administered only if clinically indicated. The inclusion criteria of the study were: (1) patients that underwent stent placement for renal/ureteral stones and returned for cystoscopical stent removal, (2) age between 20 and 85 years old, and (3) providing informed consent. Exclusion criteria were: (1) absolute or relative contraindication to ketorolac or dexamethasone, (2) acute or chronic renal failure (estimated glomerular filtration rate <50), (3) history of GI bleeding or peptic ulcer disease, (4) elevated risk of bleeding including cerebrovascular bleeding, hemorrhagic diathesis, use of any anticoagulants, or any bleeding disorder, (5) systemic infections or cerebral malaria, (6) use of live or live-attenuated vaccines, (6) concurrent use of NSAIDs or corticosteroids, (7) pregnancy, and (8) breastfeeding.

Intervention

Patients were randomized into three study groups: (1) Ketorolac group (K group), which received an intramuscular injection of ketorolac (ketorolac tromethamine, 30 mg in 1 mL) and an intramuscular injection of 1 mL of 0.9% normal saline within 30 minutes of stent removal, (2) Ketorolac and Dexamethasone group (KD group), which received an intramuscular injection of ketorolac (Ketorolac tromethamine, 30 mg in 1 mL) and dexamethasone (Dexamethasone phosphate, 8 mg in 2 mL) within 30 minutes of stent removal, and (3) Placebo group (P group), which received two intramuscular injections of 1 mL of 0.9% normal saline. A blind, qualified nurse performed the Injections. Stents were removed by an experienced urologist, with concurrent use of 2% lidocaine gel instilled per urethra.

Outcome and safety

All patients were assessed 1 and 7 days after stent removal. The primary outcome measure of the study was the score of visual analog scale (VAS) at time of the assessment. The secondary outcome measures were use of opioid medication, urgent pain-related clinical encounters in the emergency department, subjective renal colic symptoms since the stent removal, missed days of work, and injection complications.

Sample size

For sample size calculation, an effect size of 0.25 on the VAS score was considered. With a power of 80% and a type 1 error of 0.05, the sample size was calculated to be 169 (53 in each group).

Randomization, allocation concealment, and blinding

A computer application was utilized to create randomization codes. An impartial individual, uninvolved in the study, employed permuted randomized blocks for randomization. Allocation concealment involved sealed opaque envelopes numbered sequentially. Patients and nurses, surgeons, as well as the statistician, remained unaware of the treatment assignments. Ketorolac, dexamethasone, and placebo injections were indistinguishable in terms of shape, size, color, and odor. The concealment details were disclosed following the final follow-up of the last patient.

Statistical methods

Statistical Package for the Social Sciences (SPSS) statistic 20 (IBM corporation, USA) was employed for data analysis. The data analysis followed the intention-to-treat (ITT) approach, and missing data were addressed using the last observation carried forward (LOCF) method. Categorical variables were represented as frequency (percentage), while continuous variables were presented as mean (standard deviation; SD). One-way ANOVA was used to compare the VAS scores between study groups. Bonferroni method was used for post hoc test. Chi-square or Fisher's exact tests were employed to compare categorical variables. Statistical significance was defined as a P-value less than 0.05.

Results

Study flow and clinical characteristics

Fig. 1 illustrates the study flow. Out of 266 patients screened, 147 were randomized into three groups of 49 each. There were no losses to follow-up, and all 147 patients completed the study and were included in the final analysis.

Table 1 presents the baseline demographic and clinical characteristics of the patients across the three study groups: the combination group (K + D), the ketorolac-only group (K), and the placebo group. The mean age of participants was similar across the groups (P = 0.300). Gender distribution showed no

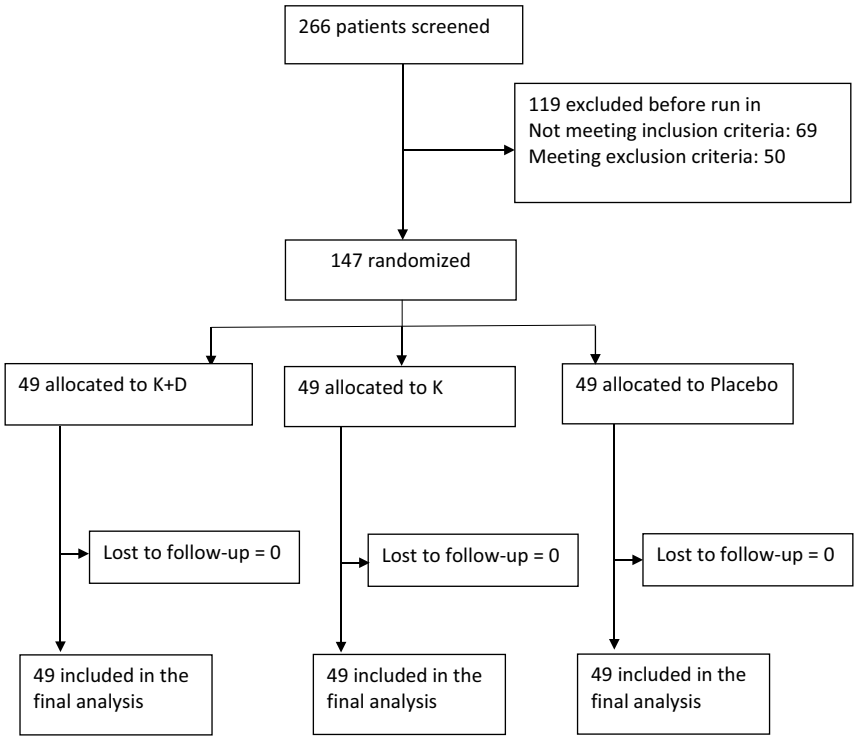

Figure 1. Flow diagram of the study.

significant differences, with the male-to-female ratio being comparable (P = 0.472). The mean BMI was also similar across the groups, with 28.2 (±3.4) kg/m^2 in the K + D group, 27.5 (±4.3) kg/m^2 in the K group, and 28.6 (±3.8) kg/m^2 in the placebo group (P = 0.375). The ASA scores, which assess the physical status of patients, were not significantly different among the groups (P = 0.491).

Baseline urological and surgical characteristics

Table 2 details the baseline urological and surgical characteristics of the patients. The mean stone size was 9.73 (±2.53) mm in the K + D group, 9.95 (±2.15) mm in the K group, and 10.55 (±2.38) mm in the placebo group, with no significant difference observed (P = 0.213). Stone location varied, but the differences were not statistically significant (P = 0.151). The stent duration prior to removal was also similar among the groups, with means of 9.95 (±3.57) days in the K + D group, 8.83 (±2.86) days in the K group, and 8.91 (±3.33) days in the placebo group (P = 0.170). Additionally, there were no significant differences in the laterality of the stones or the size of the stents used among the groups (P = 0.229 and P = 0.665, respectively).

Table 1

Baseline demographic and clinical characteristics of the patients in study groups

	K + D group (n = 49)	K group (n = 49)	Placebo group (n = 49)	P-value
Age [years; mean (SD)]	52.2 (8.0)	55.0 (9.7)	53.2 (9.0)	0.300[a]
Sex				0.472[b]
• Male	28 (57.1%)	31 (63.3%)	25 (51.0%)	
• Female	21 (42.9%)	18 (36.7%)	24 (49.0%)	
BMI [kg/m^2; mean (SD)]	28.2 (3.4)	27.5 (4.3)	28.6 (3.8)	0.375[a]
ASA score [mean (SD)]	1.87 (0.90)	2.06 (0.82)	2.07 (0.89)	0.491[a]

P-value of < 0.05 was considered statistically significant.
SD: standard deviation.
[a]One-way ANOVA.
[b]Chi-square test.

Primary and secondary outcome measures

Table 3 summarizes the primary and secondary outcomes measured in the study groups. The mean VAS score at 24 hours was significantly lower in the K + D group (2.95 ± 1.99) compared to the placebo group (4.30 ± 1.93) (P = 0.008) (Fig. 2). Post-hoc analysis indicated significant differences between the K + D and placebo groups (P = 0.006), but not between the K group and placebo (P = 0.238) or the K + D and K groups (P = 0.505). The percentage of patients with VAS scores ≥7 at 24 hours did not differ significantly among the groups (P = 0.265). Opioid use at 24 hours was also not significantly different (P = 0.123).

At day 7, VAS scores and the proportion of patients with VAS scores ≥7 were similar across groups (P = 0.571 and P = 0.773, respectively). The number of missed workdays showed a trend towards fewer days in the K + D group (2.89 ± 1.58) compared to the placebo group (3.67 ± 1.61), but this was not statistically significant (P = 0.051).

Notably, the K + D group had significantly fewer emergency department encounters (2.0%) compared to the placebo group (22.4%) (P = 0.010). The occurrence of subjective renal colic

Table 2

Baseline urological and surgical characteristics of the patients in study groups

	K + D group (*n* = 49)	K group (*n* = 49)	Placebo group (*n* = 49)	*P*-value
Stone size [mm; mean (SD)]	9.73 (2.53)	9.95 (2.15)	10.55 (2.38)	0.213[a]
Stone location (*n* (%))				0.151[b]
• Renal	16 (32.7%)	22 (44.9%)	27 (55.1%)	
• Ureteral	9 (18.4%)	11 (22.4%)	9 (18.4%)	
• Renal and ureteral	24 (49.0%)	16 (32.7%)	13 (26.5%)	
Stent duration [days; mean (SD)]	9.95 (3.57)	8.83 (2.86)	8.91 (3.33)	0.170[a]
Laterality (*n* (%))				0.229[b]
• Left	15 (30.6%)	8 (16.3%)	14 (28.6%)	
• Right	20 (40.8%)	22 (44.9%)	14 (28.6%)	
• Bilateral	14 (28.6%)	19 (38.8%)	21 (42.9%)	
Fr stent size (*n* (%))				0.665[b]
• 6	39 (79.6%)	42 (85.7%)	39 (79.6%)	
• 5	10 (20.4%)	7 (14.3%)	10 (20.4%)	

P-value of < 0.05 was considered statistically significant.
SD: standard deviation.
[a]One-way ANOVA.
[b]Chi-square test.

was also significantly lower in the K + D group (2.0%) compared to the placebo group (20.4%) (P = 0.017). Injection complications were rare and evenly distributed across all groups (P = 0.999). No other adverse events were noted.

Discussion

Pain and lower urinary tract symptoms are common after ureteroscopic stone removal due to indwelling stents. Although many patients experience relief once the stent is taken out, some suffer from acute renal colic shortly afterward. This pain is likely caused by a temporary blockage due to ureteral spasm or swelling[3]. These occurrences highlight the importance of effective pain management strategies following stent removal to enhance patient recovery.

In our study, we examined the effectiveness and safety of intramuscular ketorolac and dexamethasone in preventing renal colic after stent removal. We randomized 147 patients into three groups: the combination group (K + D), the ketorolac-only group (K), and the placebo group. Our results showed that the K + D group had significantly lower VAS scores at 24 hours compared to the placebo group, indicating effective pain relief. Moreover, the K + D group had fewer emergency department visits and lower incidences of subjective renal colic, highlighting the potential benefits of this combined treatment.

This study is novel because it investigates the synergistic effects of dexamethasone and ketorolac for post-stent removal pain. Dexamethasone, a potent corticosteroid, has strong anti-inflammatory and analgesic properties, reducing edema and inflammation in the ureter. Ketorolac, an NSAID, provides pain relief by inhibiting cyclooxygenase (COX) enzymes, which lowers pro-inflammatory prostaglandin production. Combining these two drugs might offer superior pain management compared to opioids, which, despite being effective, carry higher risks of addiction and other adverse effects[3,6,8,9].

Previous research supports the role of dexamethasone and ketorolac in postoperative pain management. For instance, a meta-analysis by De Oliveira *et al* showed that perioperative dexamethasone significantly reduces postoperative pain and opioid requirements without increasing the risk of infection or delayed wound healing[10]. Similarly, studies have highlighted that ketorolac effectively reduces renal colic and the need for emergency department visits[3].

Comparing our results to previous studies, we find both similarities and differences. Our study suggests that adding dexamethasone enhances pain relief and reduces emergency department visits. Kaiser *et al* found that dexamethasone alone could lower postoperative pain and opioid use, supporting our findings on the combination therapy's effectiveness[9].

Other studies have investigated different drug combinations and their effects on post-stent removal pain. Gangkak *et al* demonstrated that both silodosin and diclofenac significantly reduced pain after stent removal compared to placebo. However, the combination of diclofenac and silodosin did not show a statistically significant improvement over either drug alone[11]. Tadros *et al* found that a single dose of an NSAID,

Table 3

Primary and secondary outcomes measures in study groups

	K + D group (*n* = 49)	K group (*n* = 49)	Placebo group (*n* = 49)	*P*-value	Post -hoc
VAS score at 24 hours [mean (SD)]	2.95 (1.99)	3.55 (2.38)	4.30 (1.93)	0.008[a]	K + D vs K: 0.505 K + D vs P: 0.006 K vs P: 0.238
VAS score ≥7 at 24 hours (*n* (%))	3 (6.1%)	7 (14.3%)	8 (16.3%)	0.265[b]	–
Opioid use at 24 hours (*n* (%))	7 (14.3%)	15 (30.6%)	14 (28.6%)	0.123[b]	–
VAS score at day 7 [mean (SD)]	1.96 (1.64)	2.16 (1.54)	2.31 (1.68)	0.571[a]	–
VAS score ≥7 at day 7 (*n* (%))	1 (2.0%)	1 (2.0%)	2 (4.1%)	0.773[b]	–
Missed work [days; mean (SD)]	2.89 (1.58)	3.26 (1.46)	3.67 (1.61)	0.051[a]	–
Emergency department encounters (*n* (%))	1 (2.0%)	7 (14.3%)	11 (22.4%)	0.010[b]	–
Subjective renal colic (*n* (%))	1 (2.0%)	6 (12.2%)	10 (20.4%)	0.017[b]	–
Injection complications (*n* (%))	1 (2.0%)	1 (2.0%)	1 (2.0%)	0.999[b]	–

P-value of < 0.05 was considered statistically significant.
SD: standard deviation.
[a]One-way ANOVA.
[b]Chi-square test.

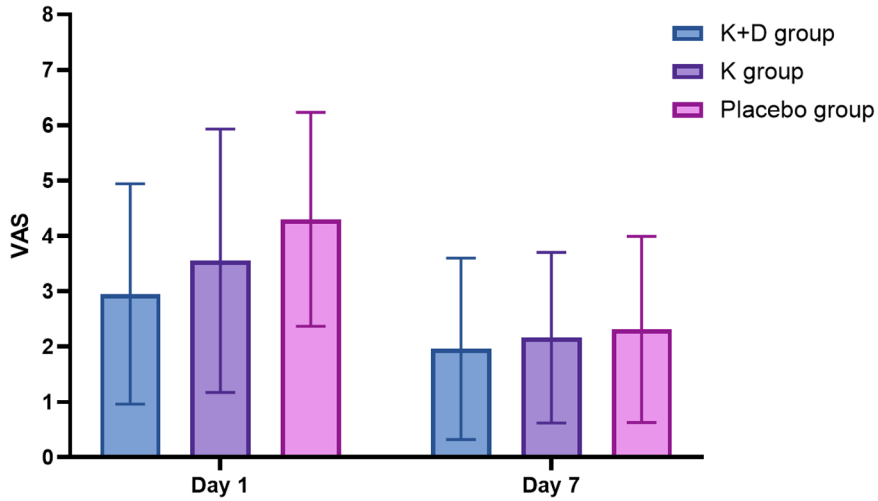

Figure 2. VAS scores at day 1 and day 7 for study groups.

such as rofecoxib, effectively prevented severe pain after ureteric stent removal, highlighting the potential benefits of NSAIDs in this context[12].

A recent study by Johnson *et al* on the efficacy of intramuscular ketorolac for preventing renal colic post-stent removal provides additional insights[3]. In their randomized controlled trial, 124 patients were administered either intramuscular ketorolac or a placebo prior to stent removal. Their findings revealed that, although ketorolac did not significantly reduce overall subjective pain scores post-stent removal, it significantly lowered the incidence of severe renal colic requiring emergency department visits compared to the control group. This aligns with our findings that ketorolac contributes to reducing emergency visits due to renal colic but also underscores the enhanced benefit when combined with dexamethasone, as shown in our study with lower VAS scores and fewer emergency encounters in the K + D group compared to placebo.

We must acknowledge the strengths and limitations of our study. The randomized triple-blind, placebo-controlled design is a significant strength, minimizing bias and ensuring robust data. Additionally, the substantial number of participants (147 patients) improves the study's generalizability. Nonetheless, we could not include the preplanned number of patients into the study. Also, the lack of long-term follow-up limits our ability to assess the prolonged effects of the drug combination. Moreover, focusing on a single clinical setting may limit the findings' applicability to other contexts or populations. Finally, we did not include a dexamethasone arm in this trial. A follow-up study could include a dexamethasone only arm to investigate its effects.

Conclusion

In conclusion, our study provides strong evidence that intramuscular ketorolac and dexamethasone effectively reduce post-stent removal pain and related complications. The synergistic effect of these drugs offers a superior alternative to opioids, potentially transforming pain management strategies for patients undergoing ureteroscopic stone removal.

Ethics approval

The protocol of the trial was approved by the Ethics Committee of CFBCR (approval code: CFBCR.REC.2023019) and the study was performed in accordance with the Declaration of Helsinki and its subsequent revisions.

Consent

Written Informed consent was provided by all patients.

Sources of funding

None.

Author's contribution

S.M., R.M., and P.H. conceptualized the idea and designed the study. S.F., M.F., A.A., and M.F.S. contributed to the data collection. S.M., R.M., and P.H. undertook the statistical analysis. S.M., R.M., S.F., and M.F. wrote the first draft of the manuscript. M.N. supervised the data analysis and significantly contributed to the manuscript. Besides, all authors drafted and provided important intellectual content for the manuscript and also all authors reviewed and approved the final version of the manuscript.

Conflicts of interest disclosure

All authors have no conflict of interest related to this work to report.

Research registration unique identifying number (UIN)

The study was prospectively registered at the ISRCTN registry (https://www.isrctn.com/; registration number: ISRCTN14221501).

Guarantor

Mohammadreza Noroozi.

Provenance and peer review

Not invited.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy.

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