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Efficacy of Intramuscular Ketorolac for Preventing Renal Colic Post Stent Removal: Randomized Controlled Trial

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Study Need and Importance: A significant portion of patient morbidity from kidney stone surgery stems from the placement of a ureteral stent. A nontrivial percentage of patients report significant renal colic immediately following the stent removal. We aim to determine whether routine administration of an intramuscular nonsteroidal anti-inflammatory agent (ketorolac) at the time of stent removal reduces this incidence of renal colic by performing a randomized controlled trial.

What We Found: A total of 124 patients were randomized to receiving a 30 mg injection of intramuscular ketorolac versus placebo saline (62 patients in each arm). While subjective measures of post-stent removal colic were no different between groups, we found that there were significantly fewer renal colic-related unplanned emergency department/clinic visits in the treatment group (2%) compared with the control group (13%, $p=0.032$).

Limitations: Inherent variations in stone composition, stone number, number of passages through the ureter to remove fragments and use of a ureteral access sheath may affect postoperative pain and lead to differences in outcomes. Likewise, a higher number of pre-stented patients in the treatment group versus the control group (15% vs 5%), although not statistically significant, could impact the degree of ureteral edema or spasm post stent removal. It is possible that awareness of post-stent removal renal colic introduced by participation in the study contributed to patients seeking medical attention when they otherwise would not have. Finally, although in most cases 6Fr stents were placed, this was neither mandated nor uniform in this study.

Interpretation for Patient Care: The placement of ureteral stents, while necessary in most cases, is the source of significant patient discomfort. While most of the discomfort is experienced while the stents are in place, a significant number of patients experience flank pain immediately following stent removal (thought to be due to transient spasming of the ureter). In a randomized trial, we found that routine administration of an intramuscular nonsteroidal anti-inflammatory agent (ketorolac) reduce the chance a patient would require an emergency room visit or unplanned urgent clinic visit.

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Efficacy of Intramuscular Ketorolac for Preventing Renal Colic Post Stent Removal: Randomized Controlled Trial

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Purpose: The treatment of stones ureteroscopically is associated with postoperative pain, thought to be due largely to the use of ureteral stents. In some, stent removal precipitates renal colic that can last from minutes to hours. We sought to determine if intramuscular ketorolac could reduce post-stent removal renal colic.

Materials and Methods: We performed a prospective, randomized, double-blind, placebo-controlled trial assessing the effects of ketorolac administered at time of stent removal. Patients were randomized to receive an intramuscular ketorolac 30 mg or placebo immediately prior to stent removal. Patients were contacted 1 and 7 days after stent removal to assess pain, need for opioids, emergency department or clinic visits and the need for surgical/medical interventions.

Results: A total of 124 patients (62 patients each in the control and treatment groups) were included in the study. The groups were comparable in demographic/operative characteristics. No difference in mean pain scores or proportion of patients who experienced severe pain at 1 and 7 days post stent removal was detected between groups. However, use of ketorolac resulted in significantly fewer renal colic-related unplanned emergency department/clinic visits in the treatment group (2%) compared with the control group (13%, p=0.032).

Conclusions: Although administration of ketorolac prior to stent removal does not significantly reduce overall subjective pain experienced post stent removal compared to placebo, it does reduce the likelihood of severe renal colic requiring emergency department or office visits. Eligible patients may benefit from routine use of ketorolac injection at the time of stent removal.

Key Words: ureteroscopy, ketorolac, renal colic

Abbreviations and Acronyms

ED = emergency department
NSAID = nonsteroidal anti-inflammatory drug
URS = ureteroscopy
VAS = visual analog pain scale

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Conflict of Interest: The Authors have no conflicts of interest to disclose.

Ethics Statement: This study received Institutional Review Board approval (IRB no. STU 012018-080). All human subjects provided written informed consent with guarantees of confidentiality.

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While the pain associated with acute stone passage has been well documented in the literature, historically less consideration has been given to the pain associated with surgical treatment of stones.[1] However, the prevalence of nephrolithiasis continues to rise in the United States, climbing to 9% in the last decade from 5.2% between 1988–1994.[2,3] Recently, increased attention has been focused on improving health-related quality of life for patients with nephrolithiasis.[4] Ureteroscopy (URS) is currently the most common procedure used to treat stones,[5,6] but patients often experience significant pain and discomfort post-procedure, thought to be due largely to use of a ureteral stent.[7] A number of investigators have assessed the efficacy of several pharmacological agents to reducing stent-related pain, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), alpha blockers, anticholinergics and opioids.[8,9] Furthermore, some have devised post-procedure medication regimens that have eliminated the need for opioid

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analgesics and rely more heavily of NSAIDs and other medications to control post-procedure stent-related pain.[10]

However, we have noted that some patients experience acute renal colic during a 24-hour window immediately following stent removal. The etiology of this pain is unclear, but it has been attributed to transient ureteral spasm or edema leading to self-limiting ureteral obstruction. While most urologists have observed this phenomenon in the occasional patient, little has been published on the frequency of occurrence or the optimal treatment of this distressing outcome after stent removal.[11]

Ketorolac tromethamine is an NSAID medication commonly used and notably safe for acute renal colic.[12,13] Both oral and parenteral forms are available. While bioavailability of enteral and parenteral ketorolac is similar, oral ketorolac is not approved for use unless following a parenteral dose. We sought to determine whether routine administration of intramuscular ketorolac at the time of ureteral stent removal would reduce post-stent removal renal colic and associated unplanned medical encounters due to these symptoms.

METHODS

After obtaining Institutional Review Board approval (IRB no. STU 012018-080), we performed a prospective, randomized, double-blind, placebo-controlled trial assessing the effects of intramuscular ketorolac administered at the time of ambulatory stent removal (NCT04112160). All human subjects provided written informed consent with guarantees of confidentiality. We hypothesized that administration of ketorolac at the time of stent removal would yield a 50% relative reduction in subjective renal colic within the first 24 hours following stent removal. Our secondary outcome was unplanned clinical encounters.

Inclusion and Exclusion Criteria, and Stone Treatment

Adult patients between 18 and 80 years of age who underwent URS with stent placement for renal or ureteral calculi by 2 fellowship trained surgeons (JA, MP) were approached for enrollment in the study. Following URS, each patient was discharged with our standard post-URS discharge medications unless there was a specific contraindication. These include tamsulosin, oxybutynin, phenazopyridine, diclofenac, acetaminophen and tramadol. Patients were instructed to only take tramadol as a last resort. Tamsulosin was continued until 3 days following stent removal. Postoperative antibiotics were not standard and were only given if the surgeon felt they were clinically indicated. Patients were required to return to our ambulatory urology clinic for stent removal to be included in the trial, and both those undergoing stent removal cystoscopically and those for whom the stent was left on a tether were eligible for the study. Patients were excluded if they had an absolute or relative contraindication to ketorolac, including those with evidence of acute or chronic renal failure (estimated glomerular filtration rate <50), current or previous peptic ulcer disease or gastrointestinal bleeding, bleeding disorder, suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, concurrent use of any anticoagulants, allergic reaction to NSAIDs, concurrent use of aspirin or other NSAIDs, pregnancy or recent myocardial infarction.

Randomization

For patients who met inclusion criteria, informed consent was obtained at the time of URS, and they were subsequently randomized to the control or treatment arm the day of the stent removal. Randomization was accomplished using a computer-based random sequence generator. The allocation sequence was kept by a research nurse and concealed from the investigators, providers and participants involved in the study. Statistical analysis was performed by a blinded investigator. Allocation was revealed after conclusion of the study.

Medication Administration and Procedure

Patients randomized to the treatment arm received an intramuscular injection of ketorolac tromethamine (30 mg in 1 ml of 0.9% normal saline) within 30 minutes of stent removal in the clinic. Control patients received an intramuscular injection of 1 ml of 0.9% normal saline. Medication was prepared the morning of stent removal by the research nurse in charge of the randomization sequence. Injections were performed by a separate, qualified registered nurse who was blinded to the medication. Stents were removed by the nurse if on a tether or via cystoscopy performed by the urologist, both with concomitant use of 2% lidocaine jelly instilled per urethra. Patients in both arms were counseled on expectations and given warnings after stent removal.

Data Collection

Patient demographic and surgical information were collected prospectively by a blinded investigator. Patients were contacted via telephone 1 and 7 days following stent removal. Visual analog pain scale (VAS) at time of the call, need for opioid medication, unplanned pain-related clinical encounters (urology office visit, emergency department [ED] visit or surgical intervention) and missed work were recorded. Patients were asked specifically if they experienced renal colic symptoms since the stent removal ("subjective renal colic").

Statistical Analysis

Student's t-test was used to determine significance for continuous or discrete quantitative data that were normally distributed. The Mann-Whitney test was used to determine significance for continuous or discrete quantitative data that were not normally distributed. Significance for categorical variables was tested via the chi-square. The endpoints of Injection Safety and the Unplanned Encounter have categories in which the expected outcome value in the contingency table is below 5. Therefore, the Fisher's Exact test was used to test significance of these endpoints. All tests were run as 2-tailed and deemed significant if $p \leq 0.05$. The study was powered to demonstrate a 50% relative reduction in subjective renal colic 24 hours after stent removal (50% incidence in the control arm and 25% in the treatment arm). Sample size calculations indicated need for a sample size of 116

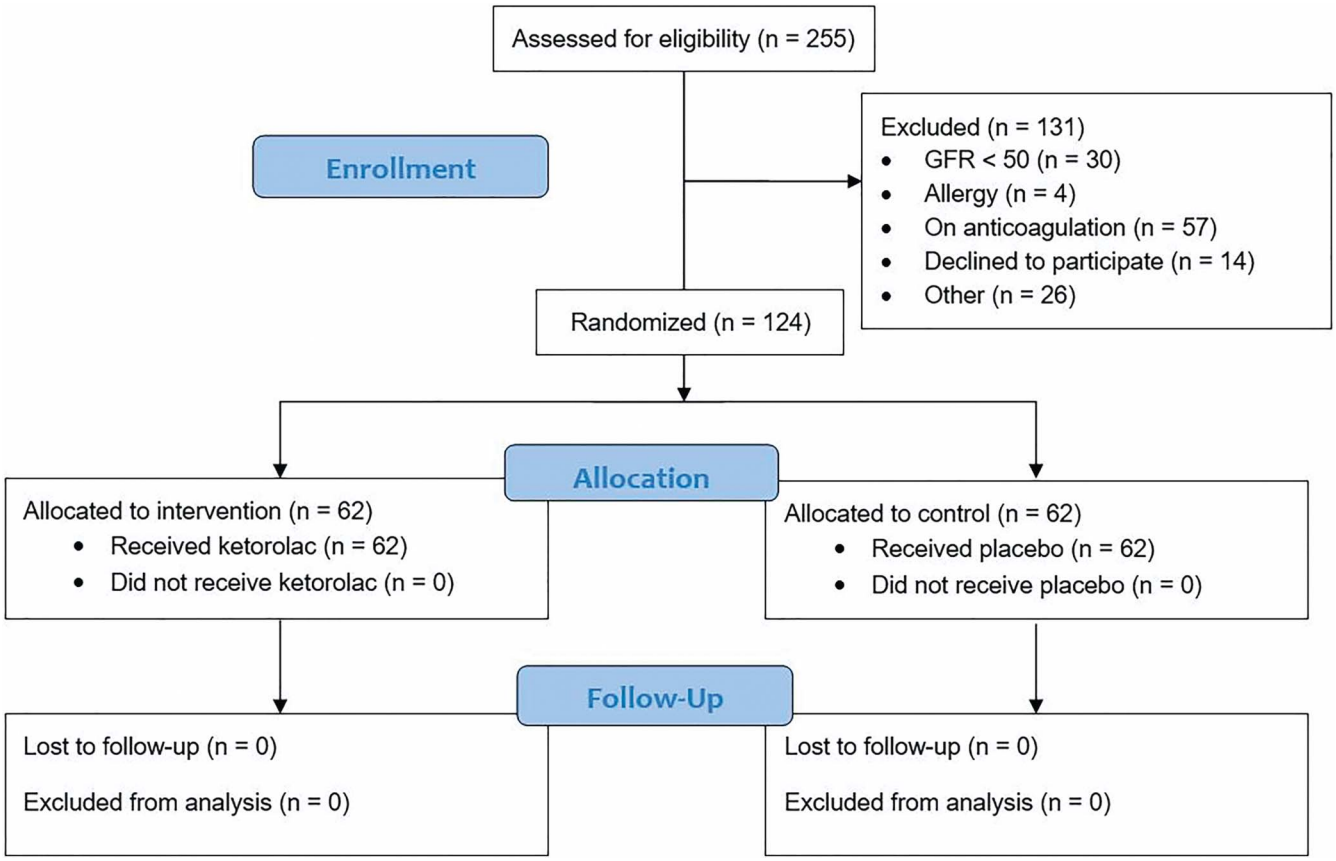

Figure. Enrollment flow diagram. *GFR,* glomerular filtration rate.

patients for 2-tailed analysis with 80% power. Data analysis was performed using SPSS® version 25 (IBM® Corporation, Armonk, New York).

RESULTS

Of a total of 255 patients undergoing URS at our university hospital during the enrollment period of April 2018 to February 2019, 210 patients were screened for enrollment. Ultimately, 124 (49%) patients who met inclusion criteria and consented to participate were enrolled and randomized into either the control group (62 patients) or the treatment group (62 patients; see Figure). The median age of the entire cohort was 56 years (IQR 47–65) and 52.4% of the patients were male. Median age, BMI, mean ASA® (American Society of Anesthesiologists®), gender, race and ethnicity were comparable between groups (Table 1).

Table 2 shows that median stone size, stone location and laterality were similar between groups. There were a higher number of pre-stented patients in the treatment group versus the control group (15% vs 5%), although this was not statistically significant. Median stent duration was 8 days for both groups. Most stents in both groups were 6Fr (89% in the control group and 82% in the treatment group, p=0.7) and were removed via cystoscopy (95% in the control group and 97% in the treatment group, p=0.6).

No statistically significant difference was detected in pain endpoints between groups (Table 3): median VAS at 24 hours (2, IQR 0–4, control group, vs 1, IQR 1–4, treatment group, p=0.6) and 7 days (0, IQR 0–1, control group, vs 1, IQR 1–4, treatment group, p=0.8). Although episodes of subjective renal colic at 24 hours were more prevalent in the control group compared to the treatment group (16% versus 10%, respectively, p=0.3), the difference did not reach statistical significance. Opioid

Table 1. *Demographic information*

	Control Group	Treatment Group	p Value
No. pts	62	62	
Median yrs age (IQR)	57 (47–65)	54 (44–66)	0.4
No. gender/total no. (%):			0.5
Female	28/62 (45)	31/62 (50)	0.5
Male	34/62 (55)	31/62 (50)	
Median kg/m^2 BMI (IQR)	28 (25–32)	30 (26–33)	0.5
Mean±SD ASA	2.2±0.6	2.3±0.6	0.5
No. race:			0.8
White	55	53	
Black	5	8	
Asian	2	1	
No. ethnicity:			0.7
Not Hispanic	58	57	
Hispanic	4	5	

Table 2. *Surgical characteristics*

	Control Group	Treatment Group	p Value
No. pts	62	62	
Median mm stone size (IQR)	7 (6–12)	8 (6–11)	0.6
No. stone location (%):			0.7
Renal	32 (52)	29 (46)	
Ureteral	12 (19)	16 (26)	
Renal and ureteral	18 (29)	17 (28)	
Median days stent duration (IQR)	8 (6–12)	8 (6–11)	0.8
No. laterality (%):			0.2
Rt	13 (21)	21 (34)	
Lt	29 (46)	20 (46)	
Bilat	20 (33)	21 (20)	
No. pre-stented prior to URS/total No. (%)	3/62 (5)	9/62 (15)	0.074
No. Fr sheath size:			0.7
9.5–11	6	5	
10/12	30	30	
12/14	16	15	
No sheath	10	12	
No. Fr stent size (%):			0.4
7	0 (0)	1 (2)	
6	55 (89)	51 (82)	
5	7 (11)	10 (16)	
No. surgeon (%):			0.084
1	37 (60)	47 (76)	
2	25 (40)	15 (24)	
No. stent removal method (%):			0.6
Cystoscopy	59 (95)	60 (97)	
Tether	3 (5)	2 (3)	

use within 24 hours of stent removal was identical between groups (27% for each).

No patient in either group developed an injection site reaction or complication. One patient in each group (1/62, 2%) complained of pain at the site of injection at the time of injection.

Our secondary endpoint was unplanned pain-related encounters. Among the control patients, 8 had an urgent visit for pain (2 clinic visits and 6 ED visits, with 1 patient requiring hospital admission). In the treatment group, a single patient presented to the ED for pain. In all cases, patients were managed conservatively with analgesia and surgical re-intervention was not required. Clinical vignettes of each return visit for both groups are presented in the supplementary Table (https://www.jurology.com). The number of ketorolac injections needed to prevent 1 unplanned pain-related visit was 9.1.

DISCUSSION

Our study showed that nearly 1 in 8 patients experiences renal colic sufficient to prompt an in-person medical encounter after stent removal, and administration of a single parenteral dose of ketorolac at the time of stent removal can reduce that occurrence by 75%.

Pain and lower urinary tract symptoms associated with indwelling stents are commonly reported by patients after URS. While most patients experience relief of these symptoms upon stent removal, some patients experience acute symptoms of renal colic shortly after stent removal, likely due to transient ureteral spasm or edema resulting in obstruction.[14] We found an incidence of delayed pain that was half that of the patients in the survey, but still occurred in 15%–16% of patients (those reporting VAS >7 at 24 hours post procedure). Furthermore, others have found that patients do not feel appropriately counseled about the risk of developing renal colic following stent removal.[11]

We sought to expand on prior studies to determine if we can mitigate peri-stent removal renal colic with administration of an intramuscular dose of ketorolac just prior to stent removal. Although we observed no difference between groups in mean VAS scores, in the proportion of patients with severe pain (VAS score ≥7) or in those with subjective renal colic symptoms after stent removal, we did observe significantly fewer unplanned, pain-related return visits in the ketorolac compared to the control group (p=0.032). It is also possible that recording VAS scores at 24 hours rather than hourly after stent removal could lack sufficient granularity to capture

Table 3. *Pain, safety and unplanned encounter endpoints*

	Control Group	Treatment Group	p Value
No. pts	62	62	
Pain endpoints:			
Median VAS at 24 hours (IQR)	2 (0–4)	1 (1–4)	0.6
No. pts with VAS ≥7 at 24 hours/total no. (%)	9/62 (15%)	10/62 (16%)	0.8
No. subjective renal colic/total no. (%)	10/62 (16%)	6/62 (10%)	0.3
No. any opioid use at 24 hours/total no. (%)	17/62 (27%)	17/62 (27%)	1
Median VAS at 7 days (IQR)	0 (0–1)	0 (0–1)	0.9
No. pts with VAS ≥7 at 7 days/total no. (%)	1/62 (2%)	2/62 (3%)	0.6
Mean±SD days missed work*	2.3±3.7	2.7±4.2	0.6
Injection safety endpoint:			
No. injection site reaction/total no. (%)	0/62 (0%)	0/62 (0%)	1
No. injection site pain/total no. (%)	1/62 (2%)	1/62 (2%)	1
No. injection complication/total no. (%)	0/62 (0%)	0/62 (0%)	1
Unplanned encounter endpoint:			
No. return to clinic or ED/total no. (%)	8/62 (13%)	1/62 (2%)	**0.032**

Bold values are statistically significant.
* Retired or nonworking individuals were excluded from this analysis.

post-stent removal pain, which may have resolved by the time of telephonic assessment.

Regardless, a reduction in unplanned urgent clinical encounters could contribute significantly to decreasing the cost burden of nephrolithiasis on the health care system and on the patient. Ketorolac is known to be safe and effective in appropriately selected patients, and while a detailed cost-effectiveness analysis would be needed to prove cost-effectiveness, at $9/intramuscular dose, use of ketorolac could potentially confer significant cost savings. However, the cost of ketorolac and its administration may vary institution to institution. Indeed, the number needed to treat (9) to prevent a single unplanned encounter is notably low. Furthermore, although the rate of subjective renal colic was statistically similar between the groups, fewer patients in the control group were prompted to initiate a clinical encounter, suggesting that those who developed symptoms post stent removal likely experienced less severity of symptoms.

Ketorolac has been shown to be a safe and effective medication in the management of patients with renal colic,[12,15] and NSAIDS have shown superiority over opioids for this indication.[1] Furthermore, when used for less than 5 days, ketorolac has been associated with a very low risk of renal failure,[16] and it has shown minimal bleeding risk even when administered after shockwave lithotripsy.[17] Ketorolac has also been uniquely formulated for intravesical instillations and embedded in indwelling ureteral stents for pain relief after URS. However, a randomized controlled trial assessing the efficacy of a ketorolac-loaded ureteral stent in reducing need for post-URS pain medications demonstrated benefit only in younger male patients between postoperative days 2–4, and no difference in pain scores after day 4 or in the number of interventions for pain were noted between control and treatment groups.[13] Another study evaluating intravesical ketorolac instillation (10 mg in 4 ml) after stent placement did show benefit in the very early postoperative period (1 hour) in the form of decreased mean flank pain scores on a symptom questionnaire.[18] Some studies have suggested that a 10 mg administration is as effective as 30 mg in managing acute pain.[19]

In a study similar to ours Tadros and colleagues performed a randomized controlled trial evaluating the benefit of a COX-2 inhibitor, rofecoxib (50 mg), given at time of stent removal.[11] With a sample size of 21 patients, they found a significant decrease in severe pain with the use of rofecoxib. However, their study outcomes were limited to pain and did not address the need for unplanned visits. Regardless, this study provided an important framework for approaching the patient experience around the time of stent removal.

Our study has several strengths. First, the study design as a prospective, randomized, double-blind, placebo-controlled trial and use of a blinded research nurse for post-stent removal VAS assessment minimized bias. Second, the study reached full power by calculation, thereby minimizing chances for a type I or type II error. However, our study also had several limitations. Inherent variations in stone composition, stone number, number of passages through the ureter to remove fragments and use of a ureteral access sheath, among other variables that affect the degree of surgical manipulation in the ureter, may affect postoperative pain and lead to differences in outcomes. Likewise, a higher number of pre-stented patients in the treatment group versus the control group (15% vs 5%), although not statistically significant, could impact the degree of ureteral edema or spasm post stent removal. It is possible that awareness of post-stent removal renal colic introduced by participation in the study contributed to patients seeking medical attention when they otherwise would not have. Finally, although in most cases 6Fr stents were placed, this was neither mandated nor uniform in our study. Nevertheless, our findings suggest that administration of ketorolac prior to stent removal may reduce the frequency of unplanned ED or office visits for acute post-stent removal symptoms.

CONCLUSIONS

Although administration of ketorolac prior to stent removal does not reduce subjective post-stent removal pain, it does reduce the likelihood of severe renal colic requiring an unplanned office or ED visit. Patients may benefit from routine use of ketorolac injection at the time of stent removal. Further evaluation is warranted to better risk-stratify patients and identify subgroups most likely to benefit from ketorolac.

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EDITORIAL COMMENT

Although a common perception that ureteral stent removal will resolve or decrease a patient's stent-related discomfort, up to 60% of patients may experience substantial pain after ureteral stent removal.[1] In fact, up to 9% of patients may seek emergency care for severe flank pain.[2] On rare occasions, stents may even need to be replaced.

Strategies to mitigate post-stent removal pain are therefore of growing interest amongst urologists. Patient morbidity, health care costs and resource utilization associated with such a simple procedure should ideally be minimal. Unfortunately, the opposite scenario is often the case for many patients. One stent removal can result in significant patient distress, numerous phone calls and unplanned visits to clinic or the emergency department (ED).

The authors performed a randomized controlled trial to assess whether ketorolac administered at the time of stent removal would reduce post-stent removal renal colic and unplanned medical encounters. No difference was observed in post-stent removal pain. However, significantly fewer patients experienced an unplanned ED/clinic visit in the ketorolac group (2%) compared to the control group (13%). These findings suggest that ketorolac does not impact the number of patients who experience post-stent removal pain, but may reduce the severity of renal colic to prevent unplanned health care encounters—an equally important outcome for both patients and providers.

Despite the well-conceived study design, there are limitations to consider. If and how nonopiate medications (eg acetaminophen, gabapentin, nonsteroidal anti-inflammatory drugs) were used in the post-procedure period was not adequately assessed. Furthermore, an unplanned ED/clinic visit for flank pain secondary to transient ureteral obstruction could have been confirmed with imaging.

Additional evidence is required to support widespread use of ketorolac at the time of stent removal. However, this medication should be considered by urologists, particularly for patients who are younger and have short indwelling stent durations, who are at the greatest risk of pain after stent removal.[3]

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REPLY BY AUTHORS

Renal colic following ureteral stent removal is commonly experienced, and inadequate patient education and patient expectation may be a contributing factor. An untreated residual stone fragment causing anatomical obstruction is always a concerning specter. Therefore, imaging in the case of severe unresolving renal colic is warranted.

In our practice, patients discharged following ureteroscopy received standardized discharge medications unless contraindicated. These include tamsulosin, oxybutynin, phenazopyridine, diclofenac, acetaminophen and tramadol (the latter to be taken only as a last resort). While the study makes an attempt to control as much as possible to minimize confounding variables that may obfuscate the role ketorolac plays, we felt it was important not to restrict or alter standard postoperative analgesia. In an effort to keep the trial protocol consistent with our standard practice, we maintained the "usual" perioperative course for the trial. Tracking actual number of medication doses taken would have provided for additional interesting data, but the logistics of data collection presented a challenge.

Recently we published the outcomes of our enhanced recovery after surgery (ERAS) protocol for ureteroscopy. While ERAS decreased the number of unplanned phone calls/messages compared to propensity-matched pre-ERAS controls, the ERAS protocol medications did not change the rate of unplanned emergency clinical encounters.[1] This would seem to indicate that modifying nonopioid perioperative medications possibly does not alter likelihood of seeking emergency care. Ultimately, we encourage the consideration of intramuscular ketorolac during office stent removal and look forward to seeing additional evidence for or against its use at other clinical centers.

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