A Novel Drug Eluting Ureteral Stent: A Prospective, Randomized, Multicenter Clinical Trial to Evaluate the Safety and Effectiveness of a Ketorolac Loaded Ureteral Stent

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Purpose: We evaluated the short-term safety and efficacy of a ketorolac loaded ureteral stent compared to a standard stent (control).

Materials and Methods: In this prospective, multicenter, double-blind study patients were randomized 1:1 to ketorolac loaded or control stents after ureteroscopy. The primary end point was an intervention for pain defined as unscheduled physician contact, change in pain medication or early stent removal. Secondary end points included medication use and pain visual analog score. A total of 20 patients underwent serum safety testing for ketorolac levels.

Results: None of the safety cohort had detectable serum ketorolac levels. Among the 276 patients there was no difference in primary (9.0% ketorolac loaded vs 7.0% control, $p = 0.66$) or secondary (22.6% ketorolac loaded vs 25.2% control, $p = 0.67$) intervention rates. Mean pain pill count at day 3 was lower in the ketorolac loaded stent group than in the control group ($p < 0.05$). A higher number ($p = 0.057$) of patients with ketorolac loaded (32%) stents used no or limited pain medications compared to controls (22%). A higher number of male patients with ketorolac loaded stents used no pain medication on days 3 and 4 compared to female patients with ketorolac loaded stents, and male and female control patients ($p < 0.05$).

Conclusions: The overall safety of the ketorolac loaded stent was confirmed. Although there was no significant difference in primary or secondary intervention rates, a trend toward a treatment benefit was noted for patients receiving drug loaded stents. Specifically young male patients appeared to require less pain medication when the ketorolac loaded stent was used. Future studies with higher drug concentrations or alternative drug eluting stents may prove beneficial.

Key Words: stents, pain measurement, endoscopy, ketorolac, ureteroscopy

Abbreviations and Acronyms

KL = ketorolac loaded

VAS = visual analog score

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Study received institutional review board approval.

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URETERAL stents are routinely used after ureteroscopy to maintain urinary flow to the bladder. Although there is debate over the necessity of ureteral stent placement after uncomplicated ureteroscopy, current endoscopic technology has not yet advanced to such a point where routine post-ureteroscopy stenting is obsolete.[1,2] The joint European Association of Urology and American Urological Association 2007 guidelines on ureteral calculi recommend ureteral stenting after ureteroscopy in patients with ureteral injury, stricture, solitary kidney, renal insufficiency or residual stone burden, and further

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state that stenting after uncomplicated ureteroscopy is optional.[1] Ureteral stents are used to relieve temporary ureteral obstruction from edema caused by endoscopic manipulation or intracorporeal lithotripsy.[1] Despite their clinical usefulness stents are not without consequences. Significant discomfort such as flank, bladder, groin and genitalia pain are all associated with the presence of ureteral stents.[3] Stent related pain has been reported by more than 80% of patients in studies.[3–5]

A wide variety of medications has been used in an attempt to treat ureteral stent discomfort. Although there are few studies comparing the various oral agents, the ones that have been conducted demonstrate minimal efficacy.[6,7] Furthermore, oral agents used in the treatment of ureteral stent discomfort have a number of significant side effects. To avoid oral medication side effects a double-blind randomized trial with intravesical instillation of agents immediately after stent placement at shock wave lithotripsy was performed.[8] A significant decrease in discomfort 1 hour after treatment in patients receiving intravesical ketorolac was noted.

Based on these findings Boston Scientific (Natick, Massachusetts) developed the Lexington™ ketorolac loaded ureteral stent in an attempt to limit stent related discomfort. Preclinical porcine studies demonstrated the safety and efficacy of the KL stent design.[9] In the current study we assessed the clinical effectiveness of the KL design compared to a standard ureteral stent.

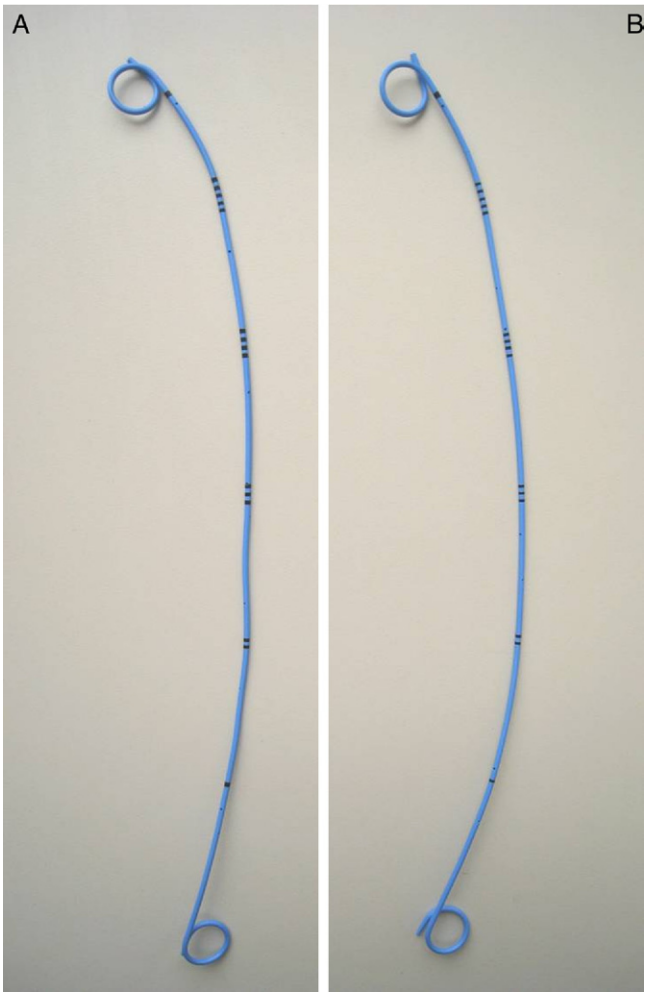

Figure 1. Percuflex Plus Double-J® ureteral stent (control, *A*) is identical to KL Lexington stent (*B*).

MATERIALS AND METHODS

The Percuflex® Plus dual pigtail stent was used as the control. The 6Fr size was used with lengths from 20 to 30 cm. The KL stent was identical to the control except that ketorolac trimethamine was loaded at 13% by weight into the base polymers (fig. 1).

The study was conducted as a prospective, multicenter, randomized, double-blinded clinical study comparing KL to control stent groups. An Investigational Device Exemption was issued by the United States Food and Drug Administration for the KL stent. After institutional review board approval was obtained at each location patients were enrolled at 14 sites (see Appendix). Men and women older than 18 years undergoing ureteroscopy for diagnosis or stone removal and requiring a ureteral stent for 4 to 10 days were eligible for the study. Women of childbearing age were required to use birth control during the study. Patients were excluded from study if they had any of the conditions of active urinary tract infection; pregnant or lactating; urinary tract malignancy within 2 years; ureteral obstruction or stricture unrelated to stones; complications of ureteroscopy; neurogenic bladder; voiding dysfunction or chronic cystitis; bilateral stents; solitary kidney; concomitant use of steroids, prescription anti-inflammatory drugs, NSAIDs or antispasmodics; gastrointestinal ulcers; renal or liver impairment; and uncontrolled hypertension.

After the uncomplicated ureteroscopic procedure randomization occurred to KL or control stent groups. Ureteral length was determined by plain x-ray of the kidneys, ureters and bladder or fluoroscopy before the procedure, measuring the distance from the renal pelvis to the ureterovesical junction. Stent position was confirmed by plain x-ray of the kidneys, ureters and bladder, or fluoroscopy and endoscopic visualization.

During the study patients were not to receive any ketorolac. However, they could receive the medication before or during the surgical procedure. Upon discharge home patients received 5 mg hydrocodone/500 mg acetaminophen to take as needed for pain. The patients kept a medication diary and recorded pain based on the validated visual analog pain scoring system.[9,10] Stents were removed by pullstring or cystoscopically. Patients were followed for 30 days after stent removal.

The primary study end point was intervention for pain, defined as an unscheduled clinic visit (or physician contact), a change in pain medication or early stent removal. Secondary end points included intervention due to stent,

Table 1. *Comparison of patient demographics*

	KL	Control	Overall
Age:			
Mean ± SD	44.59 ± 13.69	46.14 ± 13.68	45.39 ± 13.68
Minimum, median, max	18, 44, 78	19, 45, 73	18, 45, 78
No.	133	143	276
% Gender (No./total No.):			
M	54.1 (72/133)	64.3 (92/143)	59.4 (164/276)
F	45.9 (61/133)	35.7 (51/143)	40.6 (112/276)
Wt (lbs):			
Mean ± SD	189.7 ± 43.45	195.66 ± 49.52	192.79 ± 46.7
Minimum, median, max	104.3, 187, 340	102, 191.56, 420	102, 190, 420
No.	133	143	276
Ht (in):			
Mean ± SD	67.01 ± 4.18	68.54 ± 4	67.8 ± 4.15
Minimum, median, max	58, 67, 75.98	60, 68, 77	58, 68, 77
No.	133	143	276
Body mass index (kg/m^2):			
Mean ± SD	29.6 ± 5.92	29.18 ± 6.54	29.38 ± 6.24
Minimum, median, max	20.3, 28.13, 48.12	14.63, 28.08, 52.9	14.63, 28.13, 52.9
No.	133	143	276

There was no significant difference in baseline demographics between the groups ($p > 0.05$) except for height ($p < 0.01$).

pain medication use, VAS assessed pain and patient satisfaction assessed using a 5-point scale.

A safety cohort of 20 initial patients was conducted at 3 sites to assess the local and systemic impact of the KL stent. Blood and urine samples were obtained for routine chemistry studies, serum ketorolac levels and urinalysis on days 0, 1, 2, 4, 7 and 10 after placement, the day of stent removal, and days 2 and 30 after stent removal.

In terms of statistical analysis block randomization was performed at each study center to minimize error and investigator bias. Where appropriate, differences between the KL and control groups were analyzed by Fisher's exact test to compare proportions, or a t test to compare means (or the Wilcoxon rank sum test in the case of nonnormality), and declared statistically significant if $p < 0.05$. All statistical analyses were performed using SAS® for Windows®.

RESULTS

A total of 276 patients were enrolled and randomized at 14 sites in the United States between December 2005 and January 2007. There were no significant differences in demographics between KL and control groups except for height ($p < 0.01$) (table 1). Table 2 summarizes the indications and specifics of the surgical procedures in each group. Uncomplicated ureteroscopy for stone disease was the most common indication for stent placement. KL and control stents were successfully placed in all patients. Mean stent length was 25.4 cm for KL and 25.7 cm for control stents ($p > 0.05$).

There was no difference in primary interventions for KL and control groups (12/133 [9.0%] vs 10/143 [7.0%], $p = 0.66$). There was also no difference in secondary interventions between the groups (30 [22.6%] KL vs 36 [25.2%] control, $p = 0.67$), and no difference in the VAS score between the groups (mean ± SD 16.7 ± 13.2 KL and 16.8 ± 12.6 control, $p = 0.81$). The majority of patients and physicians were satisfied or very satisfied with both stents (patient satisfaction $p = 0.98$, physician satisfaction $p = 0.30$).

Patients with KL stents (32%) tended to not require pain medication after stent placement, or required medication only in the first 2 days relative to

Table 2. *Indications for ureteroscopy and details of the procedure*

	% KL (No./total No.)	% Control (No./total No.)
Purpose of ureteroscopy:		
Stone	94.7 (126/133)	95.1 (136/143)
Diagnostic	4.5 (6/133)	4.2 (6/143)
Other	0.8 (1/133)	0.7 (1/143)
Ureteroscope use:		
Flexible/sterile	38.6 (51/132)	34.5 (49/142)
Rigid	48.5 (64/132)	52.1 (74/142)
Flexible + rigid	12.9 (17/132)	13.4 (19/142)
Type of dilation:		
None required	63.2 (84/133)	60.1 (86/143)
Balloon	13.5 (18/133)	14.7 (21/143)
Rigid	19.5 (26/133)	20.3 (29/143)
Other	3.8 (5/133)	4.9 (7/143)
Procedure sheath used:		
No	56.4 (75/133)	59.4 (85/143)
Yes	43.6 (58/133)	40.6 (58/143)
Type of lithotripsy:		
Holmium laser	100.0 (77/77)	99.0 (95/96)
Other	0.0 (0/77)	1.0 (1/96)
Stone fragments left:		
No visible fragments	49.6 (60/121)	43.4 (59/136)
Residual fragment(s) 2 mm or smaller	49.6 (60/121)	52.2 (71/136)
Residual fragment(s) larger than 2 mm	0.8 (1/121)	4.4 (6/136)

Table 3. *Comparison of narcotic use*

Pain Medication Use	No. KL (%)	No. Control (%)	% Difference
None	24 (18.05)	16 (11.19)	61
On days 1 + 2 only	19 (14.29)	15 (10.49)	36
Totals	43 (32)	31 (22)	49

those with control stents (22%) ($p = 0.057$, table 3). Overall there was a 49% increase in no or limited pain medication use by the KL cohort over the control group. The average pain pill count was lower in the KL group on postoperative day 2 ($p < 0.05$, fig. 2). With gender subdivisions there were significantly more men in the KL cohort who did not require pain medication compared to the control group on days 3 and 4 ($p < 0.05$, fig. 3). Analysis of outcomes by age demonstrated those patients 45 years old or older in both cohorts used less pain medication than those younger than 45 years. Of the patients who were younger than 45 years there were more who used no pain medication in the KL group on postoperative day 4 compared to the control group, but this did not reach significance ($p = 0.08$). Of these patients younger than 45 years, those with KL stents used fewer pain pills on days 1 to 4 compared to those with control stents ($p < 0.05$). Specifically young male patients appeared to require less pain medication when the KL stent was used.

In the 20 patient safety cohort 6 had measurable plasma levels of ketorolac at some point in the study. Inadvertently 5 of these patients received systemic ketorolac before or during the surgical procedure. The sixth patient had a plasma level at day 1 after stent placement. However, the screening samples were insufficient to determine plasma or urine level of ketorolac. The levels of ketorolac detected in the 5 patients were below the steady state average plasma levels of oral and intravenous administrations of

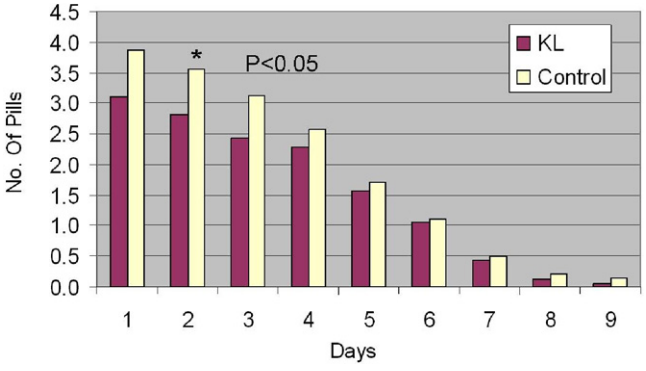

Figure 2. Comparison of mean pain pill counts after ureteral stent placement for KL and control cohorts. On postoperative day 2 only patients in KL cohort required significantly less pain medication than those in control.

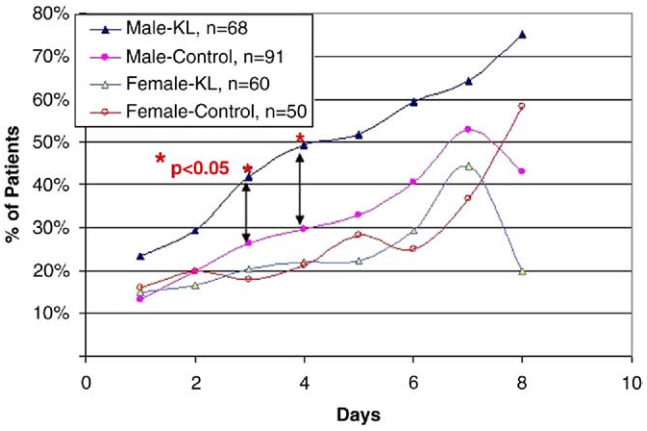

Figure 3. Comparison of number of patients who did not require pain medication by days after ureteral stent placement in KL and control cohorts, subdivided by gender. On postoperative days 3 and 4 there were significantly more men who did not require pain medication in KL compared to control cohort.

ketorolac as presented in the Physicians' Desk Reference.[11] None of the other 14 patients who did not receive systemic ketorolac had detectable plasma levels of ketorolac during the study.

Table 4 presents the device related adverse events. There was no significant difference between the KL and control group adverse events ($p > 0.05$). Device related adverse events were reported in 124 (93.2%) KL and 137 (95.8%) control group patients. The most common events were renal and bladder pain/discomfort, and voiding complaints. In the KL group there were 5 (3.8%) patients with severe adverse events requiring readmission to the hospital, including abdominal pain, urosepsis, bladder spasm, retained stone, renal colic and acute respiratory distress. The control group had 7 (4.9%) severe events including myocardial infarction, sepsis, urinary tract infection and renal colic/pain.

DISCUSSION

We report the first clinical use to our knowledge of a drug eluting ureteral stent for the management of

Table 4. *Comparison of device related adverse event rates*

	Overall	Stent Indwelling	After Removal
No. KL (%):			
Mild	53 (39.8)	54 (40.6)	4 (3.0)
Moderate	61 (45.9)	62 (46.6)	2 (1.5)
Severe	10 (7.5)	8 (6.0)	2 (1.5)
Totals	124 (93.2)	124 (93.2)	8 (6.0)
No. control (%):			
Mild	68 (47.6)	68 (47.6)	1 (0.7)
Moderate	61 (42.7)	60 (42.0)	2 (1.4)
Severe	8 (5.6)	8 (5.6)	1 (0.7)
Totals	137 (95.8)	136 (95.1)	4 (2.8)

patient discomfort. The safety of the KL stent was verified as the adverse event rates in the KL group were similar to those of the controls. Although the KL stent did not demonstrate a clear advantage in reducing the number of unscheduled physician contacts, early stent removals, pain medication changes or patient assessed pain VAS, there were trends and significant differences identified in subset analyses. Namely men and patients younger than 45 years appeared to require less pain medication when the KL stent was used compared to the control stent. The effect was most notable on days 3 and 4 after implantation.

Ureteral stents are known to cause significant patient discomfort. In our study more than 90% of patients in both treatment groups experienced some type of adverse effect related to the ureteral stent. Methods to reduce stent related adverse symptoms are important to limit unnecessary patient morbidity and health care expenditures. Studies have examined stent composition, size, length, design and position to decrease patient discomfort.[12–16] However, the ideal painless stent has yet to be identified.

Preclinical animal studies were conducted on the KL stent by Chew et al.[9] They studied 92 Yorkshire pigs, 12 of which received 5 days of oral ketorolac with control stents. For 60 days they then studied 20 each in the groups of control stent only, and 15%, 13% or 7% ketorolac eluting stent. Bladder and ureteral levels of ketorolac were associated with the dose of the indwelling stent, and none of the pigs with a KL stent had an adverse event. Serum levels were only detected in the oral ketorolac group. In the current clinical study we also demonstrated detectable serum ketorolac but only in the patients who received systemic ketorolac as a protocol deviation. Furthermore, we found no difference in adverse side effects between the KL stent and control groups.

In our subset analysis we found that younger patients consistently required more medication than those 45 years old or older regardless of treatment cohort. The KL stent appeared to limit the need for pain medication on postoperative days 3 and 4 in the younger patients. Irani et al previously reported that age was a factor in ureteral stent pain, noting that younger patients experienced more pain with stents than older individuals.[17] In contrast, Joshi et al did not find such an age stratification.[3] However, their study of 60 patients focused on the comparison of 2 scoring questionnaires rather than specific patient populations.

Since the actual mechanism of stent related pain has yet to be discerned, it is difficult to identify what drug will provide appropriate analgesia for the renal collecting system. Ketorolac has been widely used for postoperative pain in many surgical areas and was chosen for this study based on preliminary data demonstrating its short-term local efficacy.[8] It has been used for pain associated with renal colic since its introduction, so it was believed that ketorolac was likely an effective agent. It is possible that an α_1-inhibitor, anticholinergic or a local anesthetic may have a better local effect in the collecting system, and such agents would be an area for future research.

Some proposed mechanisms for ureteral stent induced pain include irritation to the bladder epithelium, ureteral spasm, aperistalsis, renal pelvis and, unlikely, renal capsule stretch. Our study focused on the presence of a foreign body as a bladder irritant. In the foreign body theory presented by Chew et al the distal curl of the ureteral stent acts as an irritant to the bladder epithelium resulting in spasm, aperistalsis and pain.[9] Other authors have attributed ureteral stent discomfort to the pressure transmitted to the renal pelvis during urination and mechanical irritation of the distal stent in the bladder.[18] The local application of ketorolac to the urothelium along the course of the stent should theoretically alleviate pain associated with local irritation. However, if the discomfort caused by the stent is actually from stretching of the renal capsule, local analgesia in the ureter would be unlikely to control patient discomfort. Specific to our study a possible mechanism for a benefit with the KL stent is vascular absorption of KL at sites of microtrauma produced during the procedure. However, the fact that plasma ketorolac levels were only detectable in patients who received systemic ketorolac in the safety cohort does not support this theory.

Another study limitation is the subjective nature of ureteral stent pain and the lack of an adequate assessment tool. The ureteral stent symptom questionnaire is the only validated ureteral stent discomfort tool available to our knowledge. However, it is designed to assess outcomes at 1 month.[19] The majority of patients undergoing uncomplicated ureteroscopy have an indwelling ureteral stent for only 2 to 10 days, making the ureteral stent symptom questionnaire an inappropriate means of assessment. Attempts to develop other pain/discomfort measurement tools have been made but are yet to be validated.[20] Thus, the current study was designed to evaluate other quantifiable end points such as unscheduled physician contact/interventions, which ultimately demonstrated no identifiable difference. We also used patient provided pill counts and the VAS score, which are problematic due to self-reporting patient variability. Ultimately the lack of an appropriate assessment tool in the current study presented a significant obstacle. Patients in the KL group often had lower assessment scores and it may even be possible that with an appropriately sensitive instrument a benefit of the KL design could be iden-

tified. If measurable differences are to be detected in future studies the issue of accurate assessment of short-term ureteral discomfort must be addressed.

Despite the limitations of the present study we note that valuable information has been obtained. Consideration should be given to focusing on high risk patients with pain, such as young males, in future studies of stent related morbidity as benefits may be more readily recognized in this cohort. In addition, a more sensitive tool is needed to accurately assess ureteral stent discomfort. We have confirmed ketorolac to be safe when applied locally to the ureter and it is plausible that a higher concentration impregnated into the stent may result in less discomfort.

CONCLUSIONS

This study demonstrates that a ketorolac eluting ureteral stent is safe with no increased risk of adverse effects compared to controls. Although this study failed to reach its primary or secondary end points, certain groups were identified within the cohort as being more likely to show a beneficial response to the KL ureteral stent. Specifically younger male patients appeared to require less pain medication immediately after surgery when the KL stent was used. Future studies should consider focusing on postoperative ureteral stent pain within 2 to 4 days of surgery in highly sensitive pain cohorts to improve the ability to discern differences between stent designs.

APPENDIX

The Lexington Trial Study Group

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EDITORIAL COMMENT

The ureteral stent is a welcome friend for the urologist but a source of pain for patients. This study investigates the potential benefits of ketorolac loaded ureteral stents and the authors have addressed a weak link in endoscopic stone surgery.

The urothelium creates an impermeable barrier due to cellular tight junctions and apical crystalline uroplakins.[1] This cellular structure has hindered the maximum potential benefits of transvesical absorption of medicines. Thus, numerous advances in transurothelial drug delivery have been investigated such as the use of protamine, chitosan, electromotive administration, hydrogels and liposomes.[2]

The clinical benefits of ketorolac coated stents are suggested but do not reach statistical significance. Local passive cellular diffusion does not appear adequate for pain control. However, vascular ketorolac absorption at sites of microtrauma and macrotrauma may be the reason the data suggest some clinical improvement. In the 20 patient safety cohort 1 patient who had not received systemic ketorolac showed positive serum levels on post-stent day 1 and no detection thereafter. Again this may be due to increased local vascular absorption at sites of inflammation, or urothelial trauma from rigid instrumentation or orificeal dilation. When subdivided by gender, male patients in the ketorolac group had the highest percentage of not requiring pain medication. A possible explanation is increased absorption from sites of trauma on the prostate. Excluding the cohort no other patient had serum levels of ketorolac tested so vascular absorption remains a hypothesis. However, an unpublished study of 92 pigs and ketorolac stents documents serum detection.[3]

A possible conclusion derived from this article is that local inflammation and trauma may allow for more absorption of ketorolac resulting in better patient comfort. It appears local passive cellular diffusion through urothelial cells is too small for clinical benefit.

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