Effect of Antihistamines on Ureteral Stent-Related Symptoms: Randomized Controlled Trial

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BACKGROUND

Study Purpose and Rationale:

Ureteral stents treat ureteral obstruction, allow for passive dilation of the ureter, maintain urine flow to the bladder, and aid in the recovery of the ureter after endoscopic surgery or ureteral injury. These stents are routinely utilized after urologic procedures for the treatment of urolithiasis and are generally kept in place for 1-2 weeks following the procedure. Despite their advantages, indwelling ureteral stents cause discomfort and reduce patient quality of life. These symptoms are partially attributed to local irritation to the ureter and bladder. Bothersome stent-related symptoms include urinary urgency, frequency, flank pain, hematuria, dysuria, sexual side effects, and emotional distress. The majority of patients with ureteral stents experience symptoms post-operatively. Several studies have indicated that agents such as antimuscarinics or alpha-1 adrenergic receptor antagonists may improve stent-related symptoms. The indications for anticholinergic medications are based on blocking involuntary bladder muscle contraction; however, the efficacy of these drugs is still controversial. Furthermore, these medications have potential adverse side effects. Antihistamines also show potential in alleviating stent-related symptoms. Multiple in vitro studies have shown H1 receptor activity involved both in ureteral peristalsis and in bladder contraction. Both first- and second-generation H1 antagonists have shown activity in the urinary tract. In clinical practice, antihistamines are commonly utilized in the management of bladder pain caused by interstitial cystitis. Additionally, a randomized controlled trial found efficacy of antihistamines for pain management in the setting of renal colic from obstructing ureteral stones. There is novel evidence that in patients with indwelling stents, there are inflammatory changes in the bladder with an associated eosinophilic reaction. Eosinophilic cystitis is commonly associated with bladder irritation or allergy, and these findings point to a novel paradigm of treating patients with antihistamines. To our knowledge, no studies have evaluated the efficacy of antihistamines for managing stent-related symptoms. We propose a randomized controlled trial to evaluate the efficacy of antihistamines in improving symptoms in patients with indwelling ureteral stents.

Research Aims & Abstracts:

Ureteral stents are routinely utilized after urologic procedures for the treatment of urolithiasis. Despite their advantages, indwelling ureteral stents cause discomfort and reduce

patient quality of life. Antihistamines show potential in alleviating stent-related symptoms. To our knowledge, no studies have evaluated the efficacy of antihistamines for managing stent-related symptoms. We propose a randomized controlled trial to evaluate the efficacy of antihistamines in improving symptoms in patients with indwelling ureteral stents.

We propose a prospective, double-blind, randomized, open label, single-center trial. 78 patients will be enrolled. Eligible participants will be adult patients (aged 18–80 years) who are undergoing unilateral retrograde ureteroscopy with planned ureteral stent placement for treatment of urinary tract stones. Eligible patients will be randomly divided into two groups in a 1:1 ratio. Group A will receive fexofenadine 180 mg once daily in addition to standard of care treatment. Group B will receive placebo in addition to standard of care treatment. The routine standard of care treatment will consist of oral NSAIDs. Results: The primary outcomes of the study are the Ureteral Stent Symptom Questionnaire (USSQ) urinary symptom score and pain score. Secondary outcomes include (i) number of office phone calls due to urinary symptoms; (ii) duration of analgesic use; (iii) duration and quantity of narcotic use; (iv) number of emergency department visits; (v) drug-related adverse effects; (vi) other domains of the USSQ.

STUDY DESIGN

We propose a prospective, double-blind, randomized, placebo-controlled, single-center trial. 78 patients will be enrolled. All patients will be provided written and informed consent. Eligible participants will be adult patients (aged 18–80 years) who are undergoing unilateral retrograde ureteroscopy with planned ureteral stent placement for treatment of urinary tract stones. The exclusion criteria are as follows: (i) preoperative use of antihistamines, beta-3 agonists, anticholinergics, corticosteroids, and chronic opioid analgesic use; (ii) preoperative indwelling ureteral stent at the time of treatment; (iii) neurogenic bladder, ureteral stricture, interstitial cystitis, or chronic prostatitis; (iv) pregnancy or breastfeeding; (v) planned bilateral ureteroscopy; (vi) solitary or transplanted kidney; (vii) hypersensitivity to antihistamines; (viii) severe renal disease (GFR < 10 ml/min or on dialysis). All patients will provide written, informed consent preoperatively. Unilateral ureteroscopic stone removal surgery will be performed under general anesthesia with a semirigid and/or flexible ureteroscope. At the conclusion of lithotripsy, a silicone double pigtail ureteral stent will be placed. Size and length of the stent will be at the discretion of the treating urologist. Patients will be excluded and will not be randomized if: (i) a ureteral stent

is not deemed necessary; (ii) there is a significant deviation in the operative plan involving a urologic malignancy or tandem stent placement (two stents in one ureter); (iii) a second-stage procedure for further stone treatment is required.

Following surgery, eligible patients will be randomized into one of two groups in a 1:1 ratio using varying block sizes. The randomization table will be built by a biostatistician and sent directly to the pharmacy who will be responsible for treatment allocation. The patients and the treating urologist will both be blinded to the treatment allocation. Group A will receive fexofenadine 180 mg once daily in addition to standard of care treatment. Group B will receive placebo in addition to standard of care treatment. The study drug will be taken starting on the evening of surgery (post-operative day #0) and will continue until the stent is removed. The routine postoperative standard of care treatment will consist of oral non-steroidal anti-inflammatory agents (NSAIDs). This treatment will be modified as needed on an individualized basis based on contraindications to these medications. If patients require further pain medication, narcotics will be considered on a limited basis depending on individual patient requirement, as per the standard of care, and the amount used will be tracked. Patients will be asked to keep a record of their analgesic usage. Anticholinergic medications may also be prescribed in the postoperative period for patients with significant bother by urinary urgency and frequency. If these medications are prescribed, their usage will also be tracked. Alpha blockers will not be prescribed routinely, but they will be continued in patients who take them chronically. The timing of ureteral stent removal will be determined based on physician and patient preference and will routinely be 1-2 weeks after surgery.

All patients will complete the Ureteral Stent Symptom Questionnaire (USSQ) three times: at their preoperative office visit, at the time of stent removal, and at their follow-up visit after stent removal. At the time of stent removal, patients will also report their usage of NSAIDs, anticholinergics, and narcotics. Patients will also be asked about drug-related adverse effects. The clinical research coordinator will contact patients every 2-3 days to assess for side effects, to maintain compliance to protocol, and to ensure patients are maintaining medication logs.

The primary outcomes of the study are the USSQ urinary symptom score and pain score. Secondary outcomes include (i) number of office phone calls due to urinary symptoms and pain; (ii) duration of NSAID use; (iii) duration and quantity of narcotic use; (iv) number of emergency department visits; (v) drug-related adverse effects; (vi) other domains of the USSQ.

STATISTICAL PROCEDURES

Sample size calculations were determined based on a previous meta-analysis investigating the effect of alpha-antagonists in reducing ureteral stent-related discomfort (Lamb et al, BJU Int, 2011). This study included five randomized controlled trials, four of which were placebo controlled. The study found a difference of 8.4 points in the Ureteral Stent Symptom Questionnaire (USSQ) urinary symptom score (mean 20.0, SD 5.6 vs. mean 28.4, SD 6.2) and a difference of 7.2 points in the USSQ pain score (mean 11.9, SD 10.1 vs. mean 19.1, SD 10.9) in the treatment group compared to the control group. Assuming a similar treatment effect, a t-test with a two-sided significance level of 0.05 will require a sample size of 35 patients in each group to detect a difference in the pain score between the two groups with a power of 80%. A sample size of 35 is larger than required to detect a difference in the urinary symptom score with the same power. Assuming a drop-out rate of 10%, 39 patients per group will be randomized.

To compare outcomes, t-tests will be used for continuous variables, and chi-square tests will be used for nominal variables. Statistical analyses will be performed using Stata (Statacorp, College Station, TX, USA). Power and sample size calculation was performed using G*Power 3.1 (Dusseldorf, Germany).

References:

1. Aboutaleb H, and Gawish M. 2017. Correlation of Bladder Histopathologic Changes Due to Double-J Stenting to the Period of Stenting: A Preliminary Study. Journal of Endourology / Endourological Society 31(7), pp. 705–710.
2. Joshi HB, Newns N, Stainthorpe A, MacDonagh RP, Keeley FX, and Timoney AG. 2003. Ureteral stent symptom questionnaire: development and validation of a multidimensional quality of life measure. The Journal of Urology 169(3), pp. 1060–1064. Joshi HB, Stainthorpe A, MacDonagh RP, Keeley FX, Timoney AG, and Barry MJ. 2003. Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. The Journal of Urology 169(3), pp. 1065–9; discussion 1069.
3. Lamb AD, Vowler SL, Johnston R, Dunn N, Wiseman OJ. 2011. Meta-analysis showing the beneficial effect of alpha-blockers on ureteric stent discomfort. BJU International 108(11), pp. 1894-902.
4. Lingeman JE, Preminger GM, Goldfischer ER, Krambeck AE, and Comfort Study Team. 2009. Assessing the impact of ureteral stent design on patient comfort. The Journal of Urology 181(6), pp. 2581–2587.

5. Sivalingam S, Streeper NM, Sehgal PD, Sninsky BC, Best SL, and Nakada SY. 2016. Does Combination Therapy with Tamsulosin and Tolterodine Improve Ureteral Stent Discomfort Compared with Tamsulosin Alone? A Double-Blind, Randomized, Controlled Trial. The Journal of Urology 195(2), pp. 385–390.
6. Yilmaz E, Batislam E, Deniz T, Yuvanc E. 2009. Histamine 1 Receptor Antagonist in Symptomatic Treatment of Renal Colic Accompanied by Nausea: Two Birds With One Stone? Urology 73(1), pp. 32-6.