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Design and Challenges of a Randomized Clinical Trial of Medical Expulsive Therapy (Tamsulosin) for Urolithiasis in the Emergency Department

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Abstract

Urolithiasis or urinary stone disease has been estimated to affect about 1 in 11 Americans. Patients with urinary stone disease commonly present to the emergency department for management of their acute pain. In addition to providing analgesia, administration of drug (medical expulsive therapy) is often prescribed to assist passage of the urinary stone. In this methodology paper, we describe the design of a prospective, multi-center, randomized, double-blind placebo controlled clinical trial of the alpha-adrenergic blocker, tamsulosin, to evaluate its effectiveness as medical expulsive therapy. In addition, we describe the unique challenges of conducting a trial of this type within the setting of the emergency department.

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Keywords

urolithiasis; kidney stones; urinary stone disease; medical expulsive therapy; alpha-blocker; emergency department

Introduction

The prevalence of urolithiasis, or urinary stone disease (USD), is increasing among adults and children in the United States[1,2]. It is estimated that USD affects about 1 in 11 people in the United States[3]. Because the most common symptoms of USD include severe flank and abdominal pain, nausea, vomiting and hematuria, patients often present to the emergency department (ED) for treatment. From 2006 to 2009 there were approximately 3.6 million visits to EDs in the United States for episodes of urinary stones[4]. In addition to the direct impact on the patient, including recurrent episodes[3], the cost of treating urinary stones is substantial. Charges for ED visits for this condition were $5 billion in 2009[4].

While relieving acute pain is the immediate goal in the management of urinary stone disease in the ED, the use of drugs to promote passage of the stone(s), or medical expulsive therapy (MET), has also been advocated. Guidelines, based primarily on randomized clinical trials with a small sample size[5,6], recommend the use of MET to promote stone passage[7,8]. Among the drugs believed to promote urinary stone passage, the class of alpha-adrenergic receptor blockers (alpha-blockers) has been studied most often. A recent Cochrane Collaboration review of 32 randomized clinical trials of this drug class concluded “the use of alpha-blockers in patients with ureteral stones results in a higher stone-free rate and shorter time to stone expulsion…and should therefore be offered as part of medical expulsive therapy as one of the primary treatment modalities”[9]. However, two recent, large-scale clinical trials[10,11] failed to show a benefit of the alpha-blocker tamsulosin (the latter also failed to show a benefit of the calcium channel blocker nifedipine) to promote passage of urinary stones compared to placebo and have called into question the use of MET[12].

We describe the design of a multi-center, randomized, placebo controlled, double-blinded trial of tamsulosin in patients with urinary stones presenting to the ED (the Study of Tamsulosin for Urolithiasis in the Emergency Department-STONE) to evaluate its effect on the passage rate over a 28-day period of treatment. We also describe several challenges encountered conducting this trial in the ED setting.

Materials and Methods

Study Design

Men and women, 18 years of age or older, presenting to participating EDs with signs and symptoms of urinary stones are screened. Those with evidence of USD based on computed tomography (CT) imaging meet with study staff to review inclusion and exclusion criteria (Table 1). Eligible persons who consent to participate are randomized via a web-based system, stratified by clinical site, to either 0.4mg Tamsulosin or matching placebo using the simple urn method[13]. Participants are instructed to take their assigned medication once daily for 28 days. The need for medical follow-up and the use of analgesic medications are based

on standard clinical care at the participating EDs. The study protocol was approved by the Institutional Review Boards of the participating institutions. All participants provided written informed consent.

The primary outcome of this trial is stone passage, determined either by visualization or capture by the study participant, within 28 days of randomization. Secondary outcomes are: (1) time from randomization to urinary stone passage; (2) surgical intervention or lithotripsy; (3) complications related to the urinary stone(s) including hospitalizations; (4) length of time in pain; (5) days of work lost; (6) amount of analgesia taken (7) overall costs; (8) urinary stone passage confirmation on CT scan; and, (9) crossover to open label tamsulosin during follow-up.

Participants are contacted via phone five times during the first 30 days after randomization (days 2, 7, 15, 20 and 29) to obtain follow-up and outcome information and again at 90 days post-randomization (Table 2).

Statistical Considerations

The sample size was based on information published in a meta-analysis on the urinary stone passage rate available at the time the study was planned[5]. This metaanalysis reported a urinary stone passage rate that varied between 20% and 73% across the studies considered. Employing a two group Pearson chi-squared test with a 0.05 two-sided significance level, we estimated that a total sample size of 500 patients equally randomized to drug and placebo would result in a 90% power to detect the difference between a placebo passage rate of 45% and a drug passage rate of 60%.

During the initial planning phase of the trial an independent Data and Safety Monitoring Board (DSMB) was established by the sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The DSMB initially served as a protocol review committee, providing input on study design, and recommended a single-site pilot study to assess feasibility. As part of the assessment of feasibility, the DSMB recommended that the urinary stone passage rate among participants randomized to the placebo group be determined after 100 participants were randomized in the pilot study since the rates in the published literature varied widely. This review confirmed the original target sample size of 500 and led to an expansion of the study to additional EDs. Recruitment for the multi-center trial was initiated in August 2013 and completed in October 2016. The initial 100 patients enrolled in the pilot are included in the target sample size of 500 allowing for losses to follow-up. If covariate adjustment is necessary, logistic regression will be used.

Secondary time to event outcomes will be analyzed using life-table analyses (time to stone passage and time in pain). Secondary dichotomous outcomes (confirmation of stone passage status on CT, need for surgical intervention or lithotripsy, repeat ED visits or other hospitalizations, crossover to open label tamsulosin, return to work, side effects, adverse events) will be analyzed using standard parametric and nonparametric statistical techniques, such as the Chi-square test.

Categorical outcomes (number of days lost from work, amount of analgesia taken, steroids taken or contraindicated medications) will be analyzed using Poisson regression with adjustment for covariates if necessary. Continuous variables will be analyzed using general linear models.

Challenges to Conducting the Study in the Emergency Department

A number of unique challenges, which may apply to other types of ED clinical research studies, were encountered in the STONE Study (Table 3). While these challenges primarily relate to engaging the participant during the recruitment process, they also have consequences for adherence to the study protocol, including the post-ED treatment regimen and data collection during follow-up. First, we recognized that in contrast to other types of clinical trials that may identify potential study participants in a non-acute illness state through physician referral, advertising, patient databases, etc., patients with USD present themselves to the ED in need of immediate care, especially pain relief. Thus, the willingness of a person with urinary stones in acute distress to be enrolled in a clinical trial may be reduced significantly. Second, there may be limited time between when both the pain is controlled and a diagnosis of USD is confirmed and when the patient is discharged from the ED. Consequently, study staff may have limited time to explain the study to the patient, answer questions about the demands of the trial, and obtain written informed consent. This time pressure is exacerbated by the fact that the ED encounter is the only opportunity for eligibility screening and randomization. Because there may be insufficient time to establish a “personal” relationship with the potential study participant, the expectation of adherence to treatment and need for follow-up contact (only remote follow-up contact is performed) may not be as firmly established as in other recruitment settings. Third, study staff must collaborate with other ED staff, urologists and radiologists to avoid treatment with the study drug or other contraindicated medications, to identify subjects with planned intervention or hospitalization for urinary stones, and to be aware of the need for CT imaging as a prerequisite for inclusion. Finally, initial interest in participation may wane after discharge from the ED and resolution of symptoms thereby hindering follow-up contacts and the ability to obtain the primary outcome. Although not specific to the ED, the unwillingness to use CT scan as the primary imaging study for abdominal pain suspected to be caused by a stone by physicians and patients was another challenge.

Discussion

The STONE Study is the first large-scale multi-center clinical trial of MET in the United States. The decision to evaluate the alpha-adrenergic blocker tamsulosin was based on the benefits of this drug to promote urinary stone passage shown in previous small clinical trials, a low frequency of adverse events, and ease of dosing (no titration)[5,14,15].

Although guidelines for the use of MET have been established, it has recently been shown to be used in about only one in five patients in the United States with urinary stones[3,16]. The reason(s) for this low rate is unclear. Recently, two large clinical trials of MET found no benefit overall[10,11]. Among 1,167 participants with a single urinary stone presenting to 24 hospitals in the United Kingdom (the Spontaneous Urinary Stone Passage Enabled by Drugs

–SUSPEND Trial) randomized to either tamsulosin, nifedipine or placebo, no significant difference in the proportion of patients requiring further intervention at 4 weeks was observed[10]. An Australian study of 403 patients presenting to five EDs found no significant difference in the rate of urinary stone passage at 28 days among persons randomized to tamsulosin compared to placebo[11]. However, in a planned subgroup analysis (n=77) of patients with large urinary stones (5 to 10 mm), the passage rate was significantly higher in patients assigned to tamsulosin (83.3%) than placebo (61.0%).

During the recruitment period of the STONE Study, the results of SUSPEND[10] were reported to the DSMB. The DSMB recommended that the STONE Study continue to enroll participants as planned due to differences in the primary outcomes between SUSPEND (need for further intervention) and the STONE Study (self-reported stone passage). The DSMB also considered the results of the study by Furyk et. al.[11] and concluded that the STONE Study should continue to recruit to target goal given that most of the study participants had already been enrolled.

There are several notable features of the STONE study. First, our primary outcome of urinary stone passage is the most direct outcome for successful medical expulsive therapy. Second, the target sample size results in 90% statistical power to detect an absolute difference of the passage rate between drug and placebo of 15%. Third, the planned sample size was not altered after evaluating the passage rate of the placebo group after 100 participants were enrolled in a pilot study. Fourth, regular telephone contact during follow-up is intended not only to foster collection of necessary information on outcomes but also to promote treatment adherence. Fifth, when possible, our primary outcome of self-reported urinary stone passage is confirmed by a repeat CT scan at Day 29. Finally, given the substantial number of patients seen annually in EDs for urinary stones, the use of the ED site for study recruitment is appropriate. In conclusion, the results of this trial will add high level evidence to inform the use of MET with an alpha-adrenergic receptor blocker in the clinical management of patients with urinary stone disease seen at the time of presentation of acute symptoms.

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Abbreviations

CT	computed tomography
DSMB	Data and Safety Monitoring Board

ED	emergency department
MET	medical expulsive therapy
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
USD	urinary stone disease

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Table 1

Inclusion and Exclusion Criteria

Inclusion Criteria
• **Age ≥ 18 years**
• **Evidence of ureterolithiasis on CT, which does not include stones located solely in the kidney**
• **Willingness to participate and able to proceed with standard outpatient management**
• **Has a telephone in order to be contacted for follow-up.**
Exclusion Criteria
• Desire or need for immediate surgical intervention
• Current urinary tract infection (based on clinical symptoms, urine dipstick, or urinalysis)
• Known anatomical genitourinary abnormalities or prior genitourinary surgeries
• Known or suspected pregnancy
• Breastfeeding mothers
• History of hypersensitivity to Tamsulosin
• Current use of any alpha blockers or calcium channel blockers
• Current use of steroids (may have an independent effect on stone expulsion)
• Spontaneous stone expulsion prior to discharge from the ED
• Largest stone dimension greater than or equal to 9mm on CT scan
• Previous treatment for the current ureteral stone
• Ipsilateral, transplanted or solitary kidney (hospitalization may be necessary)
• Known renal insufficiency
• Fever >101.5°F
• **Tamsulosin contraindications:**
○ Current use of vardenafil
○ Floppy iris syndrome
○ Planned cataract surgery in the next 60 days
• Prisoners/wards of state
• Prior enrollment in the study
• Non-English speaker due to telephone follow-up
• **Bladder stone (any stone in the bladder)**

Table 2

Follow-up Phone Contacts

	Day 2	Day 7	Day 15	Day 20	Day 29	Day 90
Study drug taken	X	X	X	X	X	-
NSAIDs taken	X	X	X	X	X	-
Percocet taken	X	X	X	X	X	-
Other analgesics taken	X	X	X	X	X	-
Stone captured	X	X	X	X	X	X
Returned to work	X	X	X	X	X	X
Side effects	X	X	X	X	X	X
PCP for follow-up	X	X	X	X	X	X
Urologist for follow-up	X	X	X	X	X	X
Return ED visits	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X
Surgical interventions	X	X	X	X	X	X
CT scan	-	-	-	-	X	-

Table 3

Challenges Encountered

Challenge	Reason	Approach to Mitigate
Missing disqualifying criteria in potential study participants (possible protocol violation)	Information presented by patient in pain, not having the ability to access all patient medical records in a timely manner.	Systematic approaches to identifying all potentially eligible persons (e.g., electronic database). Continuous communication with treating physicians about study eligibility criteria.
Recruitment including explaining the study and obtaining informed consent	Potential participant is experiencing pain. Short period of time between confirmation of diagnosis and discharge from the ED	Careful assessment of the state of the patient by study team (ability to comprehend).
Revisiting the requirements of the study during follow-up contacts (including treatment regimen, contact schedule and follow-up CT)	Randomized participant may see little value in follow-up treatment if acute pain episode resolves. Little opportunity to forge relationship with study team during screening.	Clear explanation of the importance of urinary stone passage and potential benefit of study drug to promote passage at screening and subsequent contacts. Incentives (e.g., monetary) following contacts and/or follow-up CT.
Collaboration of specialties (emergency medicine, urology, radiology)	Recruitment depends on identifying patients who are not taking tamsulosin, not being admitted and not planning to receive an intervention. Follow-up CT needs to be coordinated.	Build strong relationships with other health care workers within the ED.