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Off-label Use Tamsulosin in the Presence of Uncomplicated Radiographically Proven Distal Urolithiasis

Abstract
Background: The impact that distal urolithiasis has on patients can be devastating in terms of discomfort, pain, and overall therapy cost. Traditional first-line treatment for ureteral stone less than 5mm has been conservative therapy consisting of watchful waiting with the main focus placed on pain management. Larger stones in the range of 5mm-10mm have a significantly smaller chance of spontaneous stone expulsion with conservative therapy, many times requiring more invasive therapies such as single wave lithotripsy and uteroscopy. Although these invasive procedures are classified as "minimally invasive", and have advanced considerably in terms of technology and technique over the past 20 years, they still carry with them risks and a high cost to the patient. Over the years, researchers have isolated an abundance of alpha receptors in the distal ureter similar to those in the male prostate. The blockage of these receptors in the presence of benign prostatic hypertrophy, causes relaxation of the prostate thus increasing the ease by which voiding occurs decreasing the intra-luminal pressure. Likewise, the alpha 1 receptors present in the distal ureter have similar implications to that of the prostate in terms of ureteral relaxation, theoretically increasing the possibility for stone expulsion and reducing renal colic caused by the increased peristaltic movement in the presence of a kidney stone.

Hypothesis: The administration of the off-label use of tamsulosin with traditional conservative urolithiasis therapy will increase the facilitation in the presence of radiographically proven distal ureteral calculi in adults when compared to traditional conservative therapy.

Study Design: Exhaustive search of available medical literature.

Methods: An exhaustive literature search was performed using three main search databases: Medline- Ovid, CINAL, and PubMed. The search terms: Urolithiasis, tamsulosin, and Randomized Controlled trial were used with a limit to retrieve studies published after 2007.

Results: A total of five articles addressing evaluating the use of 0.4mg tamsulosin versus conservative therapy were used during this study. The primary endpoint addressed, was stone expulsion, because of its direct correlation with therapeutic success. Other clinically relevant and important endpoints such as: total time until stone expulsion, pain, and medication side effects were also evaluated in order to appraise the effectiveness of tamsulosin in the presence of distal ureteral stone.

Conclusion: All of the articles evaluating the first-line therapy of tamsulosin in the presence of radiographically proven urolithiasis of less than 1 cm in the adult population illustrated a statistically significant increase in stone expulsion in the 0.4 mg tamsulosin daily administration groups versus conservative therapy groups. Additionally, the secondary endpoints addressed in this study: time to expulsion, pain, and side effects of medication administration demonstrated consistent evidence suggesting positive clinical effectiveness with the use of tamsulosin as a first-line therapy.

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Off-label Use Tamsulosin in the Presence of Uncomplicated Radiographically Proven Distal Urolithiasis

Winslow Lewis

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Professor Anya Hill
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC

Biography

Born in Princeton, New Jersey to two wonderful parents who to this day remiss about their six-year-old son stopping league soccer games to make sure his teammates' medical needs were met after the occasional kicked shin or scraped knee. After 18 years of living in on the East Coast, Horace Greeley's famous New York Tribune editorial message, "Go west young man", propelled him in that very direction out to Denver, Colorado. In Colorado, Win spent four wonderful years at the University of Denver attending classes, playing lacrosse, and discovering the beauty of the mountains and adventures waiting for him on his front doorstep. It was that same passion for the outdoors which brought him back to the woods of Vermont. There, his experience on the Stratton Mountain ski patrol led to the rediscovery of his enthusiasm for taking care of patients. He enrolled in paramedic school in Boston which enabled him to gain valuable experience working the streets of the Boston area and Boulder, Colorado. After he decided to get into clinical medicine, Win's application was accepted to Pacific University for the 2009 class.

Abstract

Background: The impact that distal urolithiasis has on patients can be devastating in terms of discomfort, pain, and overall therapy cost. Traditional first-line treatment for ureteral stone less than 5mm has been conservative therapy consisting of watchful waiting with the main focus placed on pain management. Larger stones in the range of 5mm-10mm have a significantly smaller chance of spontaneous stone expulsion with conservative therapy, many times requiring more invasive therapies such as single wave lithotripsy and uteroscopy. Although these invasive procedures are classified as "minimally invasive", and have advanced considerably in terms of technology and technique over the past 20 years, they still carry with them risks and a high cost to the patient.
Over the years, researchers have isolated an abundance of alpha receptors in the distal ureter similar to those in the male prostate. The blockage of these receptors in the presence of benign prostatic hypertrophy, causes relaxation of the prostate thus increasing the ease by which voiding occurs decreasing the intra-luminal pressure. Likewise, the alpha 1 receptors present in the distal ureter have similar implications to that of the prostate in terms of ureteral relaxation, theoretically increasing the possibility for stone expulsion and reducing renal colic caused by the increased peristaltic movement in the presence of a kidney stone.

Hypothesis: The administration of the off-label use of tamsulosin with traditional conservative urolithiasis therapy will increase the facilitation in the presence of radiographically proven distal ureteral calculi in adults when compared to traditional conservative therapy.

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Conclusion: All of the articles evaluating the first-line therapy of tamsulosin in the presence of radiographically proven urolithiasis of less than 1 cm in the adult population illustrated a statistically significant increase in stone expulsion in the 0.4 mg tamsulosin daily administration groups versus conservative therapy groups. Additionally, the secondary endpoints addressed in this study: time to expulsion, pain, and side effects of medication administration demonstrated consistent evidence suggesting positive clinical effectiveness with the use of tamsulosin as a first-line therapy.

Keywords: Randomized control trial, distal ureteral stone, urolithiasis, medical expulsive therapy, tamsulosin.

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Curt, I cannot even begin to tell you how much the love and unwavering support of a best friend meant through these two and a half years. No matter where I am in mind, body or spirit, you are the guy I look to… my ace.

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To all the friends I have had the pleasure to come across during this long and wonderful journey. The lessons learned from each and every one of you turned me into the man I am today. Thank you all.

To the Pacific University PA class of 2009, without your late nights, early mornings, laughter, and hugs, I am not sure what would have happened. There could not have been a better group of guys and gals out there to learn medicine with.

And finally Andrea, you are my shining light at the beginning, middle, and end of the day, for that I owe you more than you know. I love you my dearest friend, high wings always.

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List of Abbreviations

MET……...…Medical expulsive therapy

DUS…….....Distal ureteral stone

CT…….Conservative therapy

NSAID…….Non-steroidal anti-inflammatory

SWL……Single wave lithotripsy

BPH…….Benign prostate hypertrophy

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Introduction and Background

The Oxford Text Book of Medicine states that urolithiasis is certainly not a new urologic pathology. The earliest evidence of the disorder is the stones found in mummies entombed in the predynastic Egyptian era, around 4000 BC. More recently, in the last two centuries, urolithiasis was highly associated with children, particularly boys, and was thought be correlated with poor nutrition. Although urolithiasis, secondary to poor nutrition, in Western countries has declined significantly over the past 100 years, an area of the Middle East which stretches from Jordan, through Iraq, Iran, and the Indian subcontinent to the furthest reaches of South-East Asia still has a considerable number of cases of urolithiasis stemming from poor nutrition.[1]

Although the epidemiology and etiology of urolithiasis has shifted over the last 100 years away from children and towards the adult population, and from poor nutrition to dietary over indulgence, respectively, alas urolithiasis is a is still present today. A 2006 article printed in the American Academy of Family Physicians' peer reviewed journal, reports that American men are twice as likely as women to develop calculi, with the first episode occurring at an average age of 30 years. Women have a bimodal age of onset, with episodes peaking at 35 and 55 years. Without preventive treatment, the recurrence rate of calcium oxalate calculi increases with time and reaches 50 percent at 10 years. [2] The research's insinuation that the trend in urolithiasis epidemiology is towards a younger patient population and to crossing gender boarders is concerning both at the patient level and on the macro scale.

Urolithiasis continues to be a significant problem today is seen in a variety of clinical settings. In 2003, Dellabella et al reported that urolithiasis affected about 8% to15% of the population in Europe and North America and represented the most common condition seen by urologists in the emergency

setting.[3] To further illustrate the clinical problem that urolithiasis poses, in 2006, Pearle et al conducted a study entitled Urologic Diseases in America Project: Urolithiasis, that looks at the overall effect that symptomatic ureteral stones have on the macro level. The study stated physician office visit rates for patients with a primary diagnosis of urolithiasis, as determined by the National Ambulatory Medical Care Survey, were stable between 1992 and 1996, and then increased significantly in 1998 and 2000. Ultimately, their study concluded that the patient visit rate was 43% higher in 2000 than it had been in 1992, and the total number of visits almost doubled between 1992 and 2000, increasing from 950,000 to 1,825,000.[4] The implications of the fore mentioned statistics are both, overwhelming and significant, when taking into account patient pain, sequelae of extended urolithiasis, and the medical cost accrued from the beginning of symptoms to stone expulsion. In 2000 alone, the total annual direct cost of urolithiasis in the United States was estimated at nearly $2.1 billion, including $971 million for inpatient services, $607 million for physician office and hospital outpatient services, and $490 million for emergency room services.[5] The obvious question that arises after assessing these statistics is: Is there a better, non invasive, cost effective, therapy that can be incorporated in the passage of urolithiasis?

Urolithiasis and nephrolithiasis pathophysiology is complex and may arise from a variety of medical co-morbidities and dietary factors, but the fundamental pathologic aspect of the disorder is the supersaturation of urine with stone-forming calcium salts collected within the working units of the kidney.[6] The stones eventually follow the same anatomic pathway as urine, and travel distally down the ureter many times causing the classic symptoms of renal colic and hematuria. Some patients may present asymptomatically or have atypical symptoms such as vague abdominal pain, acute abdominal or flank pain, nausea, urinary urgency or frequency, difficulty urinating, penile pain, or testicular pain.[7] Symptomatic urolithiasis can be an excruciatingly painful medical problem depending on the size of the stone and is usually is dealt with in the emergency room.

Current standard treatment for urolithiasis follows the non-invasive to more invasive spectrum depending on the size of the stone and the location within the ureter. Watchful waiting with conservative analgesic therapy is the first-line in urolithiasis treatment. Non steroidal anti-inflammatory medication, such as ketorolac and diclofenac, have the possible advantage of decreasing ureteral smooth muscle tone, thereby directly treating the mechanism by which pain is thought to occur namely, ureteral spasm.[8] The contemporary guidelines state that stones 0.5 cm or less in diameter have an 80% chance of spontaneous passage, equal to 0.5 centimeters the chance is 20-50%, and for stones greater than 0.5 cm the patient should consult an urologist.[9] On the more invasive end of the spectrum, therapies such as single wave lithotripsy, ureteroscopic removal, and finally opened uterolithotomy have been the traditional second and third line treatments for urolithiasis. Although there have been vast improvement in the last 20 years with the above mentioned minimally invasive procedures for ureteral stones, there has also been a significant increase in treatment costs.[3] The cost that Dellabella et al are referencing are not only financial, rather the overall cost to the body in terms of surgical infection, post intervention pain, and other possible post surgical sequelae.

In 2004, Sigala et al published a paper entitled Evidence for the presence of alpha 1 adenoreceptors subtypes in the human ureter, showing increased density of alpha 1a adrenergic receptors in the smooth muscle of the ureter.[10] The implication of their research is crucial in terms of urolithiasis treatment. Urolithiasis migration down the ureter is modulated by the sympathetic nervous system via the alpha 1 receptors and the movement of the stone is facilitated by peristaltic movement of the tubular ureter. The pain pathway of urolithiasis arises from the increased intraureteral pressure and peristaltic muscle movements in the presence of urolithiasis. Thus, sympathetic alpha adrenergic antagonists such as tamsulosin have the ability to inhibit basal tone, peristaltic amplitude and frequency, dilating the urethral lumen and decreasing intraureteral pressure, thereby increasing the rate of fluid transport and ultimate facilitation of the passage of the stone.[11 12]

After the general assessment of intense patient discomfort, risk versus benefit of minimally invasive urologic procedures, and overall cost of urolithiasis treatment, the question still begs: if an adjunctive therapy in the form of an off-label benign prostate hypertrophy medication like tamsulosin could help with the passage of ureteral stones, should it not be prescribed? This paper will help to answer that question by primarily analyzing the direct correlation of therapeutic success, ureteral expulsion.

Purpose and Significance of Study

A systematic review of evidence based medicine articles was performed to assess and evaluate the efficacy of the alpha 1a-d receptor antagonist tamsulosin in the presence of distal ureteral stones, specifically addressing the main endpoint: stone expulsion. Other clinically significant secondary endpoints included: time to expulsion, pain, and medication administration side effects, will further illustrate the effectiveness of tamsulosin administration in the presence of distal urolithiasis. Each of the studies assessed in this paper measured the 0.4 mg daily dose of tamsulosin with conservative treatment against conservative treatment only in the adult population with radiographically proven distal urolithiasis.

There have been significant advances in minimally invasive treatments of urolithiasis expulsion; however, they have not come without a significant cost to the patient. Along with assessing these minimally invasive therapies, researchers over the past several years have evaluated various medication expulsion therapies using off-label medications with varying degrees of success.

The ultimate goal and purpose of this paper is to further continue the evaluation of MET as a first-line urolithiasis treatment modality by assessing the off-label use of tamsulosin in the presences of distal ureteral stones in the adult population. The medication's mechanism of action, blockage of the alpha receptor 1a-d, theoretically makes tamsulosin an excellent medication choice when considering the abundance of alpha 1 receptor sites in the distal ureter. This systematic review will help evaluate

this question with the use of statistically significant evidenced based medical articles by comparing the addition of tamsulosin with traditional conservative therapy against conservative therapy only, by the evaluation of the main endpoint: stone expulsion and secondary endpoints including: time to stone expulsion, medication side effects, and evaluation of pain.

The significance of proving the effectiveness of tamsulosin as a first-line therapy in distal urolithiasis therapy has the potential to drastically improve overall patient comfort by increasing stone expulsion, decrease the episodes of renal colic, time to expulsion, and reducing patient costs.

Methods

The study is a comprehensive systematic literature review. An exhaustive literature search was performed using three main search databases: Medline- Ovid, CINAL, and PubMed. The search terms: Urolithiasis (26515), tamsulosin (792), and Randomized Controlled Trial (276,289) were used to retrieve studies published after 2007. These search criteria tallied a total of eight articles pertaining to the use of tamsulosin in the presence of urolithiasis, three of which were excluded because the tamsulosin administration was in regards to a second-line treatment after single wave lithotripsy.

The inclusion criteria includes for this study were: adult population with radiographically proven uncomplicated urolithiasis in the distal third of the ureter, male and female subjects, and that the study be at least double armed (with one arm receiving both 0.4mg of tamsulosin combined with conservative therapy daily and the other arm receiving conservative treatment only). Furthermore for inclusion, the study needed to be randomized with a JADAD score of at least two, primary outcomes of stone expulsion, time to expulsion.

Excluded were: non- randomized studies, meta-analyses, systematic reviews, and tamsulosin administration in the presence of post lithotripsy. Studies with patients with the following co-morbidities were also excluded: urinary tract infection, marked hydronephrosis, multiple stones, pregnancy, concomitant alpha blocker therapy, history of ureteral stricture, and fever.

Other statistically significant articles, urological texts, and reputable medical resource websites were also reviewed and examined for their didactic and clinical importance and used as reference material in this study.

Results

This systematic review, focusing on the first-line treatment with tamsulosin in the presence of radiographically proven uncomplicated distal urolithiasis, evaluated a total of five relevant articles found with the search criteria laid out above. These articles assessed the administration of tamsulosin with CT versus conservative therapy, traditionally defined as watchful waiting with the main focus on symptomatic pain control. Moreover, the appraised literature specifically spotlighted the adult population ranging from ages 18-65 years of age.

Wang, Huang, and Chang evaluated the clinical role of the alpha 1a-1d specific blocker, for medical expulsive therapy of symptomatic lower ureteral stones with a three armed study assessing the effectiveness of the alpha blockers: tamsulosin and terazosin. The prospective randomized study consisted of 95 patients greater than 18 years of age both male and female, with radiographically proven distal urolithiasis at 6.5mm in diameter for all groups with no statistical significant difference (P=0.99) between the size of the stone nor the differences in age or gender between the three groups. Patients were then randomly divided by the urologist who treated them in the emergency room into three groups: group 1: 32 patients received 0.4mg tamsulosin daily, group 2: 32 patients received 2mg terazosin daily, and the third group: 31 patients acted as controls (conservative therapy only). All groups received conservative therapy consisting of ketorolac 10 mg three times per day, and were allowed 0.2 mg sub lingual buprenorphine as needed, and were encouraged to stay hydrated throughout the whole study. The three major outcomes that the study looked at were stone expulsion, time to stone expulsion, and the number of colic episodes as measured by pain medication administration.

Stone expulsion was observed in 26 out of 31 patients (81%) in group one, 25 out of 32 patients (78%) in group 2, and 17 out of 31 patients in group three (55%). A statistically significant difference was seen between groups 1 and 3 and 1 and 2 (P=0.05 and P= 0.02, respectively).

Time to stone expulsion was the next endpoint observed in the Wang et al. study. The average time to expulsion for group one was 6.3 +/- 2.4 days (ranging from 3-12 days), group 2 was 6.3 +/-2.1 day (ranging from 3-11 days), and group 3 10.1 +/- 3.0 days (ranging from 6-14 days). A statistically significant difference was seen between groups 1 and 3 and 1 and 2 (P=<0.05 and P= <0.0001, respectively).

Pain as measured by mean ketorolac consumption was group 1: 231mg +/- 112mg group 2: 256 +/- 112mg, and finally group 3: 347 +/- 106. A statistically significant difference was seen between groups 1 and 3 and 1 and 2 (P=<0.0001 and P= <0.001, respectively).

One patient in the tamsulosin group reported unspecified side effects, as did five patients in the terazosin group, but all patients completed the study.

The authors concluded that first line MET proved to be safe and effective with whom watchful waiting is appropriate, particularly with the administration of 0.4 mg tamsulosin daily. The treatment was shown to be safe and effective as shown by the low incidence of side effects, increased stone expulsion rate, and reduced expulsion time. Pain ratio was also significantly reduced in the patients being treated with MET.[12]

Lojanapiwat, Kochakarn, Suparatchatpan, and Lertwuttichailkul evaluated the use of tamsulosin in the presence of uncomplicated distal urolithiasis. The study was a 28 day trial comparing two different doses of tamsulosin with conservative therapy versus conservative therapy alone. The study was a randomized control study consisted of 75 adult Asian patients with radiographically proven urolithiasis in the distal ureter with stone size ranging from 4mm –10 mm in diameter. Patients were block randomized into three groups by the assistant nurse. Group 1 was the control and received 50 mg of sodium diclofenac twice per day for 10 days. Group 2 also received 50

mg of sodium diclofenac twice per day with the addition of 0.2 mg tamsulosin per day for 28 days, or until expulsion of the stone. Group 3 also received 50 mg of sodium diclofenac twice per day with the addition of 0.4 mg tamsulosin per day for 28 days, or until expulsion of the stone. There was no statistically significant difference between group one, group two, and group three in regards to age, gender, stone size (6.70+/-1.66, 6.42+/-1.48, and 6.26 +/-1.27 respectively). The major outcomes that the study looked at were stone expulsion and time to stone expulsion.

Stone expulsion was observed in 1 out of 25 patients (4%) in the CT group, 10 out of 25 patients (40%) in the low dose tamsulosin group, and 17 out of 25 patients in the 0.4mg tamsulosin group (68%). A statistically significant difference was seen between groups 1 and 2 and 1 and 3 (P=<0.001 and P= <0.001, respectively), but no significant difference between the different doses of tamsulosin.

Mean times to stone expulsion were the next endpoints observed in the study. The average time to expulsion for the CT group ranged was 23.00 days, low dose tamsulosin group was 9.30 days, and the group 3 10.76 days. A statistically significant difference was seen between groups 1 and 2 and 1 and 3 (P=<0.001 and P= <0.001, respectively), but showed no statistical difference between the tamsulosin groups.

The authors concluded that both the low dose and regular dose of tamsulosin were good first-line therapies for patients with ureteric stones of 4mm-10mm. Furthermore, the medication will help patients achieve a stone free status and reduce expulsion times with minimal side effects. The authors went on to say that although the low dose option of tamsulosin would be an adequate first-line therapy for the Asian patient population, it is worthwhile considering that they tend to have a lower mean body weight compared with Western patients.[13]

Agrawal M, Gupta M, Gupta A, Agrawal A, and Sarkari evaluated the uses the alpha blockers: tamsulosin and alfuzosin against placebo in the presence of radiographically proven uncomplicated distal urolithiasis with the stone less than 1 cm. The prospective randomized study consisted of 102

adult patients, held to the same above mentioned exclusion criteria, randomized to three groups: group one (34 patients), those receiving 0.4 mg tamsulosin daily with conservative therapy, group two (34 patients), receiving 10 mg alfuzosin daily with conservative therapy, and group three (34 patients), receiving placebo (conservative therapy only). Conservative therapy was defined as the administration of diclofenac injections intramuscularly as needed for pain. The average stone size for groups one, two and three was comparable: 6.17, 6.70, and 6.35, respectively. Outcomes followed were, spontaneous passage of the stone, time of stone expulsion, pain measured by total diclofenac dosage, and number of pain episodes.

Stone expulsion was observed in 28 out of 34 (82.3%) patients in the tamsulosin group, 24 out of 34 (70.5%) in the alfuzosin group, and 12 out of 34 (35.2%) in CT group. Both the tamsulosin and alfuzosin groups had a statistically significant greater stone expulsion than with the CT group (P=0.008 and P=0.001, respectively), but no statistical significance existed between the alpha blocker groups (P= 0.4).

Stone expulsion time was 12.3 days in the tamsulosin group, 14.5 days in the alfuzosin group, and 24.5 days in the control group. The tamsulosin and alfuzosin groups had statistically significantly shorter expulsion time compared with the control group (P=0.003 and P=0.001, respectively), but there was no significant difference between the different alpha blockers (P=0.25).

The mean number of pain episodes for the tamsulosin and alfuzosin groups was 0.58 and 0.82, respectively, significantly less that in the control group's 5.5 episodes. In terms of average diclofenac administration during the trial, the tamsulosin group required an average of 0.88 injections, the alfuzosin group required an average of 1 injection, and the control group receiving CT averaged 6.2 injections.

The authors concluded that the study proved tamsulosin and alfuozosin administration to be significantly superior to conservative therapy in resolving distal urolithiasis, reduction in time to expulsion, and providing pain relief.[14]

Porpiglia, Fiori, Ghingone, Vaccino, Billia, Morra, Rangi, and Scarpa assessed the use of tamsulosin with CT against conservative therapy only after the failure of a previous 10 days MET cycle consisting of tamsulosin and delfacort. The study was 10 days, at the end of which outcomes including stone expulsion, time to expulsion, number of colic episodes, and amount of analgesia used were assessed. If no stone expulsion occurred after the trial, invasive expulsion measures by way of ureteroscopy were performed in order to prevent extended urolithiasis sequelae.

The prospective randomized study included 91 adult patients (tamsulosin and the control groups' mean age 46 and 51 years old, respectively) with radiographically proven uncomplicated urolithiasis (tamsulosin and control groups' mean stone size 5.93 and 6.03, respectively). The above mentioned exclusion criteria included for this study was used. The patients were broken up in to two study groups: Group A (46 patients) receiving 0.4mg tamsulosin, and group B (45 patients) acting as control receiving only conservative therapy. Both groups received intramuscular injections of 75 mg of diclofenac for as needed for pain.

Stone expulsion was observed in 37 out of 46 (80%) patients in the tamsulosin group, and 22 out of 45 (49%) in the control group. The difference between stone expulsion between the two groups was statistically significant (P=<0.01).

Time to stone expulsion for groups A and B showed no statistically significant difference between the groups (P=>0.05) with a mean time of 7.1 and 5.9 days, respectively.

The mean number of acute renal colic episodes observed for the two groups was not statistically significant (P=>0.05)were 1.39 and 1.12, respectively.

The mean analgesic administration of the tamsulosin group and control group were 122.7mg and 127.4mg, respectively and was not statistically significant (P=>0.05).

The authors concluded that the administration of 0.4mg of tamsulosin in the presence of distal urolithiasis along with conservative therapy significantly increased the expulsion of stones. They went

on to comment that the data collected during this study showed that a duration of MET up to 20 days was useful in the treatment of distal urolithiasis.[15]

Abdel-Basir Sayed et al evaluated the role of tamsulosin in the first- line medical expulsive therapy in the presence of distal urolithiasis. The randomized study consisted of 90 patients greater than 18 years of age both male and female, with radiographically proven distal urolithiasis with a mean stone size of 6.4mm and 6.8mm for the two groups and no statistically significant difference between sizes of stone. Patients were then randomly divided into two groups: group A: 45 patients received 100mg of diclofenac on an as needed basis for pain and a week of 250 mg levofloxacin, group B: 45 patients received the same conservative treatment as group A, but 0.4 mg of tamsulosin was added. The three major outcomes that the study looked at were stone expulsion, time to stone expulsion, and the number of colic episodes as measured by pain medication administration.

Stone expulsion was observed in 23 out of 45 patients (11%) in CT group and 40 out of 45 patients (88.9%) in the tamsulosin group. A statistically significant difference in stone expulsion was observed between the two groups (P=0.001).

Time to stone expulsion was the next endpoint measured. The average stone expulsion time for the CT group ranged was 12.53 +/- 2.12 days (ranging from 6-22 days) and the tamsulosin group was 7.32 +/-0.78 day (ranging from 6-11 days). A statistically significant difference was seen between the two groups (P= 0.04).

Mean analgesic use in the CT group was: 2.78 vials +/- 2.7 vials (range 0-10 vials) and the tamsulosin group: 0.14 +/- 0.5 vials (range 0-2 vials). A statistically significant difference was seen in analgesic medication administration between the groups (P=<0.0001).

The number of colic pain episodes was statistically significantly lower in tamsulosin Group compared to CT group (1.53 +/- 0.25 versus 2.47 +/- 1.41 with a P=0.003).

The study stated that there were no reported cases of medication side effects in either group.

The authors concluded that the use of tamsulosin in the facilitation of passing distal ureteral stones and associated need for analgesics was an effective and safe first-line treatment option.[16]

Discussion

The objective of this systematic review is to assess the off-label effectiveness of urolithiasis expulsion with the selective alpha 1a-d antagonist tamsulosin plus conservative therapy in the adult population with radiographically proven uncomplicated urolithiasis in the distal ureter versus the current first-line treatment modality of conservative therapy alone consisting of watchful waiting with symptomatic pain control. Besides the primary endpoint of the study, secondary endpoints including: time to stone expulsion, renal colic episodes, and side effects, were assessed. These four endpoints were chosen as the focus of this systematic literature review because of their potential positive clinical ramification in the presence of urolithiasis.

Medical expulsion therapy in the presence of kidney stones has been the focus of numerous international urologic studies in years past, with the goal being recognition of the most effective medication to facilitate stone expulsion, while taking into account potential risks involved with the medications. Several medications and combinations of medications including calcium channel blockers and alpha adrenergic antagonists, with or without steroids, have been used to aid in the spontaneous passage of ureteral calculi [17]. The decision to examine the off-label uses of these medications as a first-line urolithiasis therapy came about for several reasons, the most important being the comfort of the patient and overall goal of relieving an intensely painful disorder by increasing the likelihood of stone expulsion via pharmacologic intervention, before graduating to invasive stone expulsion procedures.

Results from the five appraised articles in this study illustrate an overwhelmingly positive result in the efficacy of stone expulsion with the administration of tamsulosin in the presence of distal

urolithiasis. In addition, the secondary endpoints evaluated: time to expulsion, pain, and medication side effects also demonstrated to be both statistically significant and clinically important.

Stone expulsion

Stone expulsion is the main endpoint addressed in this article because of its direct correlation with therapeutic success. The passage of distal ureteral stones, in the above outlined patient population, was statistically significantly greater in all studies when comparing tamsulosin plus conservative therapy to conservative therapy alone(see Table 1).

Upon further tabulation of the data collected in this study, the number needed to treat was also evaluated as to better assess the clinical significance of tamsulosin administration as a first-line therapy. The NNT calculation, ranging from 1.52 to 3.30 in the five studies, illustrates impressive ratio of tamsulosin administration to stone expulsion, further demonstrating the effectiveness of this therapy (see Table 1).

The implications of the consistent positive data findings throughout recent clinical trials are important on the individual patient level in regards to a greater expectation of spontaneous stone expulsion, thus significantly increasing patient comfort by the reduction of associated intense renal colic, reducing the chance of prolonged ureteral stone sequelae, reducing invasive urologic procedures, et cetera. On the macro level, the relief of symptomatic urolithiasis by non invasive stone expulsion also has a strong impact on society as a whole in regards to cost and efficient delegation of medical personnel and resources.

Time until stone expulsion

Total time from renal colic symptoms until stone expulsion is a secondary, although, essential endpoint also addressed in this study. The intense nature of symptomatic ureteral stones and amount of time patients have to experience that pain is an important clinical consideration when addressing the decision to use the current conservative treatment versus treating kidney stones with the off-label use of tamsulosin in addition to the conservative treatment.

In four of the five appraised articles, a statistically significant reduction in expulsion time was demonstrated with the use of tamsulosin versus conservative therapy (Table 2). The implication of this consistent data finding is certainly an important assessment tool when taking into account the comfort of the patient, more specifically how much less time patients have to experience pain.

Pain

Pain is arguably, the most important clinical characteristic concomitant with ureteral stones. The difficulty for researchers lies in the actual measurement of the study participant's subjective definition of pain. Regardless of the difficultly of measurement, pain remains an essential part of the presentation of kidney stones, and is thus addressed in this systematic review.

Pain was addressed in all five of the studies evaluating the effectiveness of tamsulosin in the presence of distal ureteral stones, but was subject of varying descriptions and findings. In only four of the five studies, was pain *formally* addressed with a statistical analysis. The quantification measurement that was evaluated in these studies and that on which this systematic review chose to focus was the total amount of medication administered during the study, more specifically the administration of non steroidal anti-inflammatory medication because of its current use as a first line treatment in ureteral stone symptomatic pain control. The studies performed by: Sayed et al, Agrawal et al, and Wang et al all showed that statistically significantly less NSAID medication was administered with the use of tamsulosin plus CT when compared to conservative therapy alone. Porpiglia et al showed no statistically significant difference in NSAID administration between the two groups (see Table 3 for full results). Although the measurement is not perfect, there is certainly compelling evidence that informs the use of tamsulosin in pain reduction during urolithiasis episodes.

Side effects of medication administration

The final secondary endpoint evaluated was side effects caused by tamsulosin administration in each of the five studies assessed. As with any medication, the risk to benefits ratio must be evaluated before administration. Being a first-line treatment in the relief of BPH symptoms, the medication's

mechanism of action is as an alpha 1a-d antagonist, thus the medication does, theoretically, have side effect potential. Common side effects occurring happening in greater than 10% of patients are the following: hypotension/orthostatic hypotension, headache, dizziness, abnormal ejaculation, and infection.[18]

All of the five articles evaluated in this systematic review addressed side effects in their research, more specifically the lack of side effects. Interestingly, in all of the five studies, no patient pulled out of the study due to side effects. Furthermore, of those five studies, in three studies: Sayed et al, Porpiglia et al, and Lojanapiwat et al patients did not experience any side effects. The remaining two studies, Agrawal et al and Wang et al experienced one "adverse side effect" and "mild side effects", respectively, but did not report on what specifically the side effects were only commenting that all patients finished in spite of them. The suggestion of this data is certainly compelling when taking into account the risk versus benefit of tamsulosin as an off-label use.

Cost

Thus far, consistent positive evidence for the off-label therapeutic use of tamsulosin in the presence of uncomplicated distal ureteral stones has been illustrated by statistically significant and clinically relevant data collection from recent articles. The final concern that this systematic review will address is the cost of distal ureteral stones expulsive treatment in comparing MET to minimally invasive urologic procedures.

The cost of treating urolithiasis is approximately 2.1 billion dollars per year [5], a staggering number to say the least. Furthermore, in a 2008 Bensalah et al study assessing the cost-effectiveness of MET using tamsulosin with CT versus traditional watchful waiting observation with symptomatic pain alone control showed an $1132 cost advantage with MET using tamsulosin over traditional conservative observation ($1493 versus $2625, respectively) assuming the presumed 54% increase in stone expulsion on MET. The study went on to discuss the high cost of ureteroscopy ($4773) when compared to the low cost of tamsulosin administration ($2.08 per pill, $28 for 14 days, a normal MET

course) and stated even a 1% greater likelihood in stone passage with MET makes the therapy a cost effective strategy because it precludes the need for ureteroscopy which is 170 times more expensive than the cost of tamsulosin.[19]

Limitations

Although the evaluated articles support the administration of tamsulosin in the presence of radiographically proven distal urolithiasis in the adult population, and continuously suggests positive outcomes in regards to stone expulsion, decreased time to expulsion, decrease in pain, and few to no side effects, there were limitations to this review.

The first limitation of the study came about with the minimally specific nature of the ureteral stone size. The inclusion criteria for these studies were generally a stone greater than 4-5 mm and less than 1cm, and the measurement was then averaged for statistical data tabulation. Although there was no statistically significant difference between the experimental and control groups in terms of stone size in the included articles, in the future studies measuring specific stone sizes would aid the further assessment of tamsulosin administration.

The second limitation came in the form of potential study biases. In the five studies assessed, although all of the patients were randomized, yet there was little or no explanation as to the manner in which this was accomplished. Additionally, none of the evaluated articles were multi-centered studies. With the addition of double-blinded studies and larger studies that incorporate numerous medical facilities, the power of these trials will grow and further prove the effectiveness of tamsulosin in the presence of distal ureteral stones.

The figures outlining clinical success in the evaluated articles are compelling. Although the evidence points to positive outcomes with tamsulosin administration, more specific clinical trials including double-blinded, multi-facility trials are warranted for the further evaluation of this off-label use.

Conclusion

In conclusion, the main focal point of this systematic review was placed on stone expulsion in the presence of uncomplicated distal urolithiasis because of its direct correlation with therapeutic success. This principal endpoint has been consistently proven in the adult population with current, reputable, and reproducible clinical trials. Furthermore, additional clinically relevant data throughout the literature suggested strong evidence for a decreased time to stone expulsion, decreased pain, and a significantly increased cost-effectiveness with the addition of tamsulosin as a first-line therapy in the presence of distal ureteral stones. Tamsulosin has proven clinically efficacious and has shown few to no side effects in the evaluated clinical trials indicating that it has an excellent risk to benefit ratio as a first-line therapy in all clinical settings.

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Tables

Table 1:

Comparison chart of tamsulosin versus conservative therapy in the distal ureteral stone expulsion

Study	Expulsion (tamsulosin versus control, respectively)	P value	NNT
Agrawal et al	82.3% vs 35.2%	P=0.008	2.48
Lojanapiwat et al	68.0% vs 4.0%,	P= <0.001	1.52
Wang et al	81.0% vs 55.0%	P=0.05	3.30
Sayed et al	88.9% vs 51.1%	P=0.001	2.13
Porpiglia et al	80.0% vs 49.0%	P=<0.01	2.74

Table 2:
Comparison chart of tamsulosin versus conservative therapy in time to distal ureteral stone expulsion

Study	Time to Expulsion in days (tamsulosin versus control, respectively)	P value
Agrawal et al	12.3 days vs 24.5 days	P=0.003
Lojanapiwat et al	10.76 days vs 23.00 days	P= <0.001
Wang et al	6.3 +/- 2.4 days (ranging from 2-12 days) vs 10.1 +/- 3.0 days (ranging from 1-14 days)	P=<0.05
Sayed et al	12.53 +/- 2.12 days (ranging from 6-22 days) vs 7.32 +/-0.78 day (ranging from 6-11 days)	P= 0.04
Porpiglia et al	5.9 days vs 7.1 days	P=>0.05

Table 3:
Comparison chart of tamsulosin versus conservative therapy

Study	Pain measurement description	P value
Agrawal et al	Total pain episodes- (T vs CT) 0.58 vs 5.5 Total diclofenac injections- (T vs CT) 0.88 vs 6.2	Reported statistically significant, but no P value was reported
Lojanapiwat et al	Renal colic episodes- No difference reported between the groups	No P valuve reported reported
Wang et al	Mean analgesic dose (T vs CT) Buprenorphine administration- 0.39mg vs. 0.39mg Ketorolac consumption- 231mg vs 347mg Colic episodes 1.97 vs 2.16	 P=>0.05 P=0.0001 P= >0.05
Sayed et al	Pain episode (T vs CT) 1.53 vs 2.47 Number of analgesica vials used (T vs CT) 2.78 vs 0.14	 P=0.003 P=0.001
Porpiglia et al	No. acute renal colic (T vs CT) 1.39 vs 1.12 Total diclofenac (T vs CT) 122.7 mg vs 127.4 mg	 P=>0.05 P=>0.05

Table 4: Tamsulosin administration side effect

Study	Side effects	Did all participants complete study?
Agrawal et al	"mild"- Dizziness(4), headache (5), Fatigue(2), Rhinitis(2), retrograde ejaculation(3)	Yes
Lojanapiwat et al	No adverse effects reported	Yes
Wang et al	One adverse effected	Yes
Sayed et al	None	Yes
Porpiglia et al	None	Yes

Table 5: Evaluated article table

Author/ Title/ Journal	Yr. published	Patients/ Population	Intervention	Comparison	Outcome(s)	Study type	Validity (Jadad score)	Comments
Lojanapiwat et al/Effectiveness of Low-dose and Standard dose Tamsulosin in the treatment of Distal Ureteric Stones: a Randomized Controlled Study	2008	75 Asian patients with 4mm-10mm Uretic stones on XR	0.2 mg tamsulosin 50 mg diclofenac BID Adequate hydration for 10 days 0.4 mg tamsulosin 50 mg diclofenac BID Adequate hydration for 10 days	No A-blocker 50mg diclofenac BID Adequate hydration For 10 days	Expulsion, Time to expulsion	RCT	3	Primarily looked at Asian population. Study showed decreased expulsion time, and shown safe. 68% passage with 0.4 mg tam 40% passage with 0.2 mg tam 4% passage with placebo
Wang et al./Efficacy of an Alpha 1 Blocker in Expulsion Therapy of Lower Ureteral Stones	2008	95 patients with radiographic proof of <10 mm stone	0.4mg tamsulosin daily for 14 days 2.0mg terazosin for 14 days Both groups received 10mg ketorolac TID, SL 0.2 mg buprenorphine PRN, instructed to drink 2L	10mg ketorolac TID, SL 0.2 mg buprenorphine PRN, instructed to drink 2L H2O/day For 14 days	Expulsion rate, expulsion time, amount of pain med used	RCT	3	Statistically significant difference was seen in all three measuring parameters with tamsulosin and terazosin versus placebo in distal

			H2O/Day					urolithiasis SE experienced, but all patients finished study
Agrawal et al/ Prospective Randomized Trial Comparing Efficacy of Alfuzosin and Tamsulosin in Management of Lower Ureteral Stones	2008	102 patients w/ urolithiasis <1cm in distal ureter as seen by radiographic proof	0.4 mg tamsulosin daily 3L of H2O, 75 mg diclofenac injection PRN pain for up to four weeks 10mg alfazosin QD 3L of H2O, 75 mg Diclofenac injection PRN pain for up to four weeks	Placebo conservative treatment consisting of 3L of H2O, 75 mg diclofenac injection PRN pain	Expulsion, expulsion time, pain quantified by amount med use	RCT	2	Spontaneous stone expulsion - statistically significant difference b/w Tam and placebo statistically significant difference b/w Alfazosin and placebo Stone expulsion time- statistically significant difference b/w Tam and placebo statistically significant

								difference b/w alfazosin and placebo PAIN- Pain episodes tam- 0.52 alf- 0.82 placebo- 5.5 diclo injections tam- 0.88 alf- 1 placebo- 6.2
Porpiglia et al/ A second cycle of Tamsulosin in patients with distal ureteric stones: a prospective randomized trial	2009	91 patients with lower uretral stones between 5mm-10mm with radiographic evidence who previously failed a 10 day MET trial with daily 0.4 mg Tamsulosin	0.4 mg tamsulosin QD hydration 75mg diclofenac inj PRN	Conservative treatment- hydration 75mg diclofenac inj PRN	Stone expulsion, time to expulsion, renal colic episodes	RCT	2	Study showed statistically significance in stone expulsion, but time to expulsion and renal colic episodes was not significant between the two groups. Also study did not report any significant SE of the groups.
Sayed et al/	2008	90 adult	0.4 mg	Conservati	Stone	RC	2	Results of

Efficacy of Tamsulosin in medical expulsive therapy for distal ureteral calculi		patients with 5mm-10mm stone with radiographic evidence for four weeks	tamsulosin daily 2L of H2O/ day, 100 mg diclofenac PRN pain for up to four weeks	ve therapy- 2 L ofH2O/day hydration, 100 mg diclofenac PRN pain for up to four weeks	expulsion, time to stone expulsion, pain episodes	T		stone expulsion, time to expulsion, and pain between tamsulosin group and conservative therapy all statistically significant