MEDICAL EXPULSIVE THERAPY OF URETERIC CALCULI-OUR EXPERIENCE
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ABSTRACT: INTRODUCTION: Ureteric stones can be treated with multiple modalities including medical therapy, ureteroscopy, shockwave lithotripsy (SWS), percutaneous nephrolithotomy, open/laparoscopic stone removal, and/or combinations of these modalities. The aim is to study the effectiveness of medical management of ureteric stones and to compare the effectiveness of Tamsulosin and Tamsulosin with steroid.

MATERIALS & METHODS: 120 Patients who came with acute ureteric colic were categorized into three categories of less than 5mm, 5mm to 7mm and more than 7mm based on NCCT. They were consecutively allotted to one of the three groups, the group I patients received Anti-Biotics with NSAIDs group II received Tamsulosin in addition Anti-Biotics and NSAIDs and III rd group received Anti-Biotics, Tamsulosin, NSAIDs in addition Deflazacart 30mg for a period of 10 days. The results were evaluated at the end of 10 days medical treatment.

RESULTS: 90 out of 120 patients were re-evaluated at the end of 10 days. The calculi of <5mm get passed out spontaneously in nearly 50% and addition of Tamsulosin with or without steroid did not give any significant benefit. Spontaneous passage of calculi about 5-7mm was seen in about 40-50% and the addition of Tamsulosin or steroid did not show any significant benefit. Calculi of more than 7mm passed out in 15-20% of the patients with or without combination therapy.

CONCLUSION: The patients with ureteric calculi of <7mm should be given time (up to 4 weeks) to pass out the stone if there are no complication like sepsis. Calculi >7mm should be removed as the chances of passage is <20%. The medical treatment with Tamsulosin or Tamsulosin with Deflazacart does not offer significant benefit.

KEYWORDS: Ureteric calculi, Tamsulosin, Expulsive therapy, Deflazacort, Urolithiasis.

INTRODUCTION: The ureteric colic presenting in the emergency room accounts for approximately 50% urological emergencies. The incidence of colic and stones appears to be increasing over the past few years. The lifetime risk of kidney stones is estimated to be between 5% to 10% with the recurrence rate as high as 50%.¹ Further, the prevalence of nephrolithiasis is increasing, resulting in an ever increasing economic burden.²³

Ureteric stones can treated with multiple modalities including medical therapy, ureteroscopy, shock wave lithotripsy (SWS), percutaneous nephrolithotomy, open/laparoscopic stone removal, and/or combinations of these modalities. The choice of intervention depends on patient factors, anatomical considerations, surgeon preference and stone location and characteristics.

Medical expulsive therapy is an option preferred by most of the patients. We have tried to assess the effectiveness of the commonly prescribed Tamsulosin alone or in combination with steroids in our patients. In the majority of the cases the colic is due to calculus <5mm which may get passed spontaneously or the expulsion may be facilitated with medical treatment. The
medical treatment is given to reduce the pain, prevent infection, relax the ureter and reduce the oedema and spasm of ureter at the site of stone impaction. This is achieved by NSAID (oral or parental) to reduce the pain, anti-biotics to prevent inflammation alpha antagonist (Tamsulosin) to facilitate relaxation and dilatation of the ureter. Oral corticosteroid like Tab. Deflazacart 30mg daily once is used to relieve the spasm and oedema.

MATERIAL & METHODS: A prospective study of medical management of uretric calculi was done after obtaining the ethical committee approval. A total of 120 Patients attended the emergency of SVRRGH Tirupati from 1st July 2014 to 30th June 2015. The diagnosis and characterization of calculi was based on NCCT scan done at the time of colic. The pts were allotted to one of the 3 groups consecutively based on stone size and location. The calculi of less than 10mm only chosen for medical treatment.

Group I received Tab. Aceclofenac 100mg (NSAID) + Tab. Oflaxacin 200mg BD for a period of 10 days.

Group II received Tab. Aceclofenac 100mg (NSAID)+ Tab. Oflaxacin 200mg BD+ Tab. Tamsulosin 0.4mg HS.

Group III received Tab. Aceclofenac 100mg (NSAID)+ Tab. Oflaxacin 200mg BD+ Tab. Tamsulosin 0.4mg HS+ Tab. Deflazacart 30mg OD.

The patients with past history APD received pPI (Tab. Rabeprazole 20mg OD) in all the three groups. The stones was characterized based on size and location. Based on size stones are grouped into <5mm, 5-7mm and >7mm. Based on location there are grouped into upper, middle and lower ureteric calculi.

At the end of 10 days treatment, a repeat NCCT was done assess the expulsion rate of calculi. The patients with unrelenting pain, sepsis, and solitary kidney were excluded from the study.

RESULTS: Out of 120 pts 90 pts were enrolled for the study after exclusion of patients who developed fever (5pts) persistent pain (10pts) and 15 pts who did not turn up for followup. The site and size of calculi is shown in table 1. The calculi of less than 5 mm are commonly seen in the lower ureter29/35(83%). They are uncommon in the mid 4/35 and upper ureter 2/35.

The calculi of 5-7mm are commonly seen in the lower ureter 14/21 (66%). The remaining calculi 7/21 are equally distributed in the upper and mid ureter.

The calculus above 7mm are equally distributed in upper 11/34 and middle 10/34 and lower ureter 13/34. The overall distribution of calculi based on size is given in table-2.

The calculi of less than 5 mm calculi get passed in nearly 50% cases and appears to increase to 80% with combination treatment but the difference is not statically significant. The calculi of 5-7 mm are expelled in about 40-50% with or without combination treatment and the difference is not statically significant. The calculi of more than 7 mm are passed out in 15-20% cases with or without combination treatment and the difference is not significant.

The success rate of medical treatment in the three groups is given in table 3 and table 4.
| Treatment group | Size of the calculus | Total | P value |
|-----------------|----------------------|-------|---------|
|                 | < 5 mm | 5 – 7 mm | > 7 mm |         |
| Upper ureteric calculi |       |       |       |         |
| Group I         | 2      | 2      | 4      | 8       | 0.81; NS |
| Group II        | 1      | 1      | 4      | 6       |         |
| Group III       | 1      | 1      | 3      | 5       |         |
| Mid ureteric calculi |       |       |       |         |
| Group I         | 1      | 1      | 4      | 6       | 0.70; NS |
| Group II        | 1      | 1      | 3      | 5       |         |
| Group III       | 0      | 1      | 3      | 4       |         |
| Lower ureteric calculi |       |       |       |         |
| Group I         | 10     | 5      | 5      | 20      | 0.99; NS |
| Group II        | 10     | 5      | 4      | 19      |         |
| Group III       | 9      | 4      | 4      | 17      |         |

Table 1: Distribution of Ureteric calculi by location and size in the three treatment groups

| Group | Size of ureteric calculi | Total (%) |
|-------|--------------------------|-----------|
|       | < 5 mm | 5 – 7 mm | > 7 mm |
| Group I | 13(38.2) | 8(23.6) | 13(38.2) | 34(100.0) |
| Group II | 12(38.7) | 7(22.6) | 12(38.7) | 31(100.0) |
| Group III | 10(38.5) | 6(23.0) | 10(38.5) | 26(100.0) |
| Total (%) | 35(38.9) | 21(23.2) | 35(38.9) | 90(100.0) |

Table 2: Overall distribution of ureteric calculi based on size in three treatment groups

P=0.99; NS.

| Treatment group | Size of the ureteric calculi | Treatment success (%) |
|-----------------|--------------------------|------------------------|
|                 | < 5 mm | 5 – 7 mm | > 7 mm |          |
| Group I         | 6/13 (46.2) | 3/8 (37.5) | 2/13 (15.4) |      |
| Group II        | 7/12 (58.3) | 3/7 (42.8) | 2/12 (16.7) |      |
| Group III       | 8/10 (80.0) | 3/6 (50.0) | 2/10 (20.0) |      |
| P value         | 0.25; NS | 0.89; NS | 0.96; NS |          |

Table 3: Medical treatment success rate of ureteric calculi in three treatment groups by size of calculi

Figures in parentheses are percentages.
| Treatment group | Total no. of cases | No. of cases successful with medical treatment | Percentage |
|-----------------|-------------------|-----------------------------------------------|------------|
| Group I         | 34                | 11                                            | 32.4       |
| Group II        | 31                | 12                                            | 38.7       |
| Group III       | 26                | 13                                            | 50.0       |

Table 4: Overall treatment success of medical treatment of ureteric calculi in three treatment groups

P=0.38; NS.

DISCUSSION: Spontaneous passage of ureteral stones is dependent on stone size and location among other factors. Coll et al. demonstrated with unenhanced computed tomography that ureteral stones <5mm had a greater than 75% change of spontaneous passage regardless of location.\(^4\) Larger stones were less likely to pass (For stones 5-7mm, 60%; for stones 7-9mm 48%; and for stones larger than 9mm, 25%). Stone location regardless size was also a significant factor; spontaneous passage rates were 48% for stones in the proximal ureter, 60% for mid ureteral stones, 75% for distal stones. Miller et al. demonstrated that time to stone passage can take greater than a month but can be high as 95% in stones <5 mm in size.\(^5\)

A meta-analysis performed by the AUA/EAU guidelines panel demonstrated that for stone < 5mm, 68% of stones would pass spontaneously. For stones >5mm and <10mm, 47% would pass spontaneously.\(^6\) In those patients with no infectious parameters, adequately controlled symptoms, and smaller ureteral stones, spontaneous passage is an excellent option. Attempts at spontaneous passage stones can save a patient invasive surgical intervention as well as significant cost.\(^7\) Observation is not indicated in those patients with unremitting or disabling pain, persistent urinary obstruction, infection, solitary kidney or electrolytes abnormality with or without renal insufficiency.

Medical Expulsion Therapy: Prior to the use of calcium channel blockers and alpha antagonist, spontaneous passage was aided with increased fluid intake along with antiemetics and analgesics. Characterization of adrenergic receptors in the human ureter\(^8\) and smooth muscle physiology.\(^9\) Led to be development of targeted medical treatment.

Hollingsworth et al. published a meta-analysis in 2006 of medical treatment and its use to facilitate stone passage.\(^10\) The group analyzed a total of nine randomized controlled trails combing the results of those using calcium channel blockers or alpha antagonists to treat ureteral stones. The article demonstrated those patients given channel blockers or alpha antagonists had a 65% greater likelihood of stone passage (P<0.0001), with a number needed to treat of four patients.

More recently, the AUA/EAU guidelines panel has further analyzed all available data on the use of calcium channel blockers and alpha antagonists. The panel demonstrated that nifedipine had an absolute increase of 9% in stone-passage rates compared to alpha antagonists that had a 29% when compared to control; nifedipine.
Other authors have reviewed and corroborated the evidence that medical treatment with either class of agent facilitates stone passage.\cite{11} Singh et al. analyzed 16 studies using an alpha antagonist and 9 studies using a calcium channel blockers. Their analysis suggested that the addition of these agents compared to standard therapy significantly improved spontaneous stone expulsion. Alpha-antagonist had relative risk (RR) of 1.59 and a number needed to treat of 3.3 patients. Subgroup analysis of trails using low-dose steroids, antibiotics, and anticholinergic agent (in addition to calcium channel blockers and alpha antagonist) did not yield further benefit.\cite{11,12} Adverse effects such as transient hypotension, dizziness, headaches, and nausea/vomiting were 4% in those treated with alpha antagonist and 15.2% in those receiving calcium channel blockers.

Other investigators have demonstrated a benefit with the addition of corticosteroids. Parpiglia et al. performed a prospective study of 114 patients divided into four groups (controls, Tamsulosin alone, deflazacort alone, or a combination of Tamsulosin and deflazacort). The group receiving combination therapy had an 84% expulsion rate compared to 60% for the Tamsulosin group (P<0.05). Combined therapy with Tamsulosin and deflazacort may improve stone passage rates.\cite{13}

Hermanns and colleagues randomized 100 patients with < or = 7mm distal ureteral stones to either placebo or Tamsulosin treatment.\cite{14} Median stone size was 4.1mm for Tamsulosin group and 3.8mm for placebo group (P=0.3). Stone expulsion rates were similar between the two groups, 86.7% and 88.9%, respectively. This suggests that alpha antagonists may not increase stone passage in all cases, but may still be beneficial given its association with decreased analgesic use.

Not all alpha antagonists work the same. Most research and results were studied with tamsulosin, making it the most commonly prescribed alpha antagonist in the United States. Pedro and colleagues studied the use of alfuzosin as the agent of choice for medical expulsive therapy.\cite{15} Stone size comparable between the two groups (4.08 vs 3.83 mm). Stone passage rates were similar between the two groups, 77.1% for placebo and 73.5% for alfuzosin group. However, the alfuzosin group had less discomfort as evidenced by pain scores and also had decreased times to passage.

Alpha adrenergic receptors are present in high density within the distal ureter. There are three types of receptors in the distal ureter: 1A, 1B, and 1D. The receptor with the highest density is the 1D and therefore it is not surprising that specific antagonists to this receptor have been developed. Sun and colleagues randomized 60 patients to watchful weighting versus 50mg od naftopidil.\cite{16} The stone expulsion rate was significantly higher in the naftopidil group (90.0% vs 26.7%) and the patients had no side effects. Zhou et al. randomized 131 patients to 10 mg naftopidil daily, tamsulosin 0.4 mg daily, or watchful waiting. Both naftopidil and tamsulosin had similar stone expulsion rates (72.1% and 82.2%, respectively).\cite{17}

**PREDICATORS OF MEDICAL EXPULSIVE THERAPY SUCCESS:** In addition to the aforementioned studies on stone size and location for predicting stone passage rates, other studies have suggested imaging findings and laboratory values can be predictive of stone passage. Recently, Lee and colleagues retrospectively investigated stone passage with
Tamsulosin-based MET along with parameters on CT imaging including transverse stone diameter, longitudinal stone diameter, ureteral diameter (proximal to stone), and ureter-to-stone diameter ratio. They noted that each of these factors were inversely associated with successful stone passage, regardless of stone position within the ureter (P<0.001). Interestingly, only longitudinal stone diameter (maximal stone diameter on coronal reconstruction) was significantly associated with stone passage on logistic regression analysis. Stone expulsion rates appeared to drastically decrease at the 5mm mark measured longitudinally with 70% and 84.3% passage of 4-5mm upper and lower ureteral stones, respectively and 42.9% and 44.8% passage of 5-6mm upper and lower ureteral stones, respectively.[18]

Aldaqadossi studied 235 patients receiving MET. Stone expulsion within 4 weeks was recorded in 129 patients (54.9%), while 106 patients (45.1%) underwent ureteroscopy for stone extraction. C-reactive protein (CRP) was significantly different in the two groups; stone expulsion had significantly lower serum CRP levels (16.45+2.58) compared to those who failed (39.67+6.30). He suggested a cut-off point of 21.9mg/L for CRP with those below benefiting from MET and those above being offered immediate, minimally invasive ureteroscopy.[19] The use of laboratory values to predict stone expulsion rates is an interesting concept but needs to be further studied prior to widespread implementation.

**CONCLUSION:** Watchful waiting is required for calculi of <7mm to get passed out. The watch period may need to be extended after 4 weeks if there are no complications. The medical therapy does not give any added advantage in the expulsion of calculi of <7mm. Early intervention is advisable for calculi of >7mm.

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