A Prospective Comparative Study to Evaluate the Effect of Alpha Blocker on Ureteric Orifice for Ease of Ureteroscopy in Patients of Ureteric Calculus and BPH

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ABSTRACT

BACKGROUND

The selective alpha-blockers are widely used in the clinical treatment for ureteral stones as MET (Medical Expulsive Therapy). American Urological Association and European Association of Urology, strongly recommend that patients with ureteral stones be alpha-blockers to promote stone passage. Due to the physiological effect of alpha-blockers on the ureter, researchers hypothesized that the use of alpha-blockers before ureteroscopy may help during the Ureteroscopic procedures, making it easier and safer. One critical step in doing ureteroscopy is directing scope into vesicoureteral junction as most of the time its non-dilated and this is place injury and later stricture chances are high which lead to failure of treatment.[3] But in literature, there is a discrepancy with this hypothesis as some studies have failed to demonstrate the benefits of technical ease and lower complication rate with alpha-blocker being used in the preoperative period.

METHODS

We conducted a cross sectional study in the department of urology from January 2019 to January 2020. 30 patients of ureteric calculus on alpha-blocker therapy and 30 patients of BPH on alpha-blocker ± 5 alpha reductase therapy were included for study. During URSL (Ureteroscopic Lithotripsy) we used 6 / 7.5 fr URS (Ureterorenoscope), ease of admitting URS in vesicoureteral junction noted. The need for ureteral dilator for admitting URS, presence of mucosal injury, and bleeding or false passage noted as difficulty in instrumentation. And documentation of finding done in excel.

RESULTS

Out of 60 patients, 24 (40 %) patients didn't need dilatation of ureteric orifice and Ureteroscopy was done easily among which 8 (33.33 %) were BPH patient and 16 (66.66 %) were ureteric calculus patient this difference is statistically significant with p-value 0.010. 36 (60 %) patients needed dilatation of ureteric orifice to facilitate URS of which 22 (61.11 %) patients were from the BPH group and 14 (38.88 %) are ureteric calculus group. The study shows a statistically significant difference with p-value 0.029.

CONCLUSIONS

Our study demonstrates that alpha-blockers failed to show a statistically significant difference in relaxation of the ureteric orifice in non-ureteric calculus patients. Further large group, multi-centric studies are required to find a definitive role for alpha blockers prior to URS.

KEYWORDS

BPH, Silodosin, Ureteroscopy, Ureteric Orifice, Alpha Blocker, Alpha 1a, Medical Expulsion Therapy

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BACKGROUND

Alpha blockers form the main stay for management of ureteric calculus and its integral part of Medical Expulsion Therapy (MET). As per American urological association guidelines there is grade A recommendation for use of alpha blockers for ease of spontaneous expulsion of ureteric calculus. It has low risk profile and wide therapeutic window.[1]

Ureteroscope has come long way from being rigid ureteroscope to semi rigid ureteroscope and latest flexible scope since its inception which was in 1980.[2] Semi rigid ureteroscope has become standard of care for management of all sort of ureteric calculus. It gives certain advantages compared to its competitive counterpart such as extra corporeal shock wave lithotripsy which doesn't give direct visualisation of calculus while doing lithotripsy. Ureteroscopy is easy procedure and gives direct visualisation of calculus and lithotripsy happens under vision. One critical step in doing ureteroscopy is directing scope into vesicoureteric junction as most of the time its non-dilated and this is place of injury and later stricture chances are high which lead to failure of treatment.[3]

Use of alpha blocker has been recommended by AUA (American Urological Association) and Also Backed by many systemic meta-analyses specifically for stone less than or equal to 10 mm.[4] Alpha receptors are abundant in ureter and most concentrated in vesicoureteric junction, they help in peristalsis of ureter and causing segmental contraction of ureter. With alpha blocker this action is inhibited leading to relaxation of ureteric smooth muscle causing dilatation of ureter and ureteric orifice and decreasing the strength and frequency of peristalsis, propulsion of stone occurs due to hydration which is part of medical expulsion therapy.[5]

This effect of alpha blocker on ureteric orifice gave clue to researchers to use it for ease of ureteroscopy and reducing complication and time required for surgery.[6] But in literature, there is a discrepancy with this hypothesis as some studies have failed to demonstrate the benefits of technical ease and lower complication rate with alpha-blocker being used in the preoperative period.[3]

Alteration in alpha receptor contribute to various other diseases such as hypertension, BPH etc. Alpha 1 AR has important role in development of Lower Urinary Tract Symptoms (LUTS) in BPH (Benign Prostatic Hyperplasia) patients and so alpha 1AR antagonist are most commonly used drugs in medical management of BPH patient.[7] Lepor and associates demonstrated that the alpha 1a is predominant alpha receptor. With use of autoradiography and immunohistochemistry they found alpha 1 a receptor localised to prostate stroma. Functional studies have shown they cause contraction of prostate. So alpha blocker causes relaxation of prostate smooth muscle leading to improvement of symptoms.[8]

Our literature search failed to show studies on effect of alpha blocker on relaxation of ureteric orifice in non-ureteric calculus patient such as BPH patients. So we have proposed this study to see if alpha-blocker causes relaxation of the vesicoureteral junction and ease the ureteroscopy procedure by allowing easy admission of URS at the vesicoureteral junction and intramural portion of the ureter by comparing among patients with ureteric calculus on alpha-blocker and patient with BPH taken for TURP (Trans-Urethral Resection of Prostate) who are without ureteric calculus and are already on alpha-blockers.

We wanted to assess the effect of alpha blocker on ureterovesical junction and ureteric orifice, and assess the ease of ureteroscopy and ureteroscope negotiation at ureteric orifice.

METHODS

We conducted a cross sectional study in the Department of Urology from January 2019 to January 2020. 30 patients of ureteric calculus on alpha-blocker therapy and 30 patients of BPH on alpha–blocker ± 5 alpha reductase therapy were included for study. Patients from 18 - 70 yrs. of age were considered for the study.

Inclusion Criteria

1. All patients of ureteric calculus on alpha-blockers who failed MET.
2. All patients of BPH on alpha blocker ± 5 alpha-reductase inhibitor who planned for TURP.

Exclusion Criteria

1. Patients with VUJ (Vesico-Ureteric Junction) calculus.
2. Patients who are pre-stented for ureteric calculus.
3. Patients with a large median lobe where ureteric orifice difficult to approach.
4. History of ureteric reimplantation surgery.
5. Patients with stone size > 1 cm,
6. The spontaneous stone passage before surgery.
7. Patients with ureteral strictures and ureteral anomalies.
8. History of ureteroscopic intervention.

All patients of ureteric calculus started on alpha-blocker as the protocol of institute, and observed for two weeks, if patients show no improvement in symptoms, no change in stone position, increase in symptoms, increase serum creatinine then considered for URSL. During URSL we used 6 / 7.5 fr URS, ease of admitting URS in vesicoureteral junction noted. The need for ureteral dilator for admitting URS, presence of mucosal injury, and bleeding or false passage noted as difficulty in instrumentation. And documentation of finding done in excel.

Patients of BPH started on alpha-blocker ± 5 - alpha reductase inhibitor as per institute protocol.

a. Moderate-to-severe voiding symptoms refractory to medical therapy.
b. AUR (Acute Urinary Retention) refractory.
c. Recurrent and robust gross haematuria (after ruling out infection, carcinoma, trauma).
d. Recurrent urinary tract infections (bacterial prostatitis) (both acute and chronic) excluded.

e. Bilateral hydronephrosis with renal functional impairment (after reliving obstruction with catheterization and then optimise patient).
f. Elevated or increasing PVR. (Post Void Residual)

If any of the above is present then the patient considered for TURP. Before starting TURP bilateral ureteric orifice identified and 6 / 7.5 Fr URS admitted in the ureteric orifice. If during procedure ureteroscope is not negotiated easily then need of dilatation of ureteric orifice is considered and documented.

The values were entered into MS-Excel and statistical analysis has been done by using SPSS version 13. For categorical variables, the values are expressed as numbers and percentages, and to test the association between the two groups, Fischer exact test is used. For continuous variables, the values are expressed as mean ± standard deviation, all p-values having less than 0.05 are considered statistically significant.

RESULTS

The study included a total of 60 patients, 30 male patients of the ureteric calculus group (Group A), and 30 from the BPH group (Group B). Mean age of study population is 48.18 ± 14.83 yrs., ureteric calculus group is relatively younger with a mean age of 35.23 ± 8.53 yrs. whereas BPH has a higher mean age group of 61.13 ± 5.25 yrs. Out of 60 patients, 24 (40 %) patients didn't need dilatation of ureteric orifice and ureteroscopy was done easily among which 8 (33.33 %) were BPH patient and 16 (66.66 %) were ureteric calculus patients, this difference is statistically significant with p-value 0.010. 36 (60 %) patients needed dilatation of ureteric orifice to facilitate URS of whom 22 (61.11 %) patients were from the BPH group and 14 (38.88 %) were ureteric calculus group. The study shows a statistically significant difference with p-value 0.029. We used Fischer exact test for statistical analysis. The complication was noted in 2 patients in the BPH group and 4 patients from the ureteric calculus group.

Average calculus size of URSl group was 10.23 ± 1.5 mm. and average prostate size of BPH group was 3.35 ± 2.3 cc.

Ureteroscope Negotiation	Total	BPH Group	Ureteric Calculus Group	P-Value
• With dilatation	36 (60)	22 (61.11)	14 (38.88)	0.035 (CHI
• Without dilatation	24 (40)	8 (33.33)	16 (66.66)	Square Test)
Complication (%)	6 (10 %)	2 (6.6 %)	4 (13.3 %)	0.6707 (Fischer Exact Test)

Table 1. Need of Dilatation in BPH Vs. Ureteric Calculus Group

DISCUSSION

The role of adrenergic receptors in the human ureter was first described in 1970.[9] The a-adrenergic receptors are classified into three different subtypes: a1A, a1B, and a1D.[3] Mapping of alpha receptor on ureter have shown that distal ureter have more alpha receptor compared to other part of ureter, in vitro study of subtype of alpha receptor has shown that alpha 1D is highest concentration in distal ureter and at vesico uretric junction followed by alpha 1A and least is alpha 1B on distal ureter, and this may be the reason that alpha blocker is more effective in management of distal ureteric calculus.[7] In a study by Yasunori Itoh et al,[7] he has suggested to use alpha 1D antagonist for management of distal ureteric calculus for the very fact that these are the most abundant receptor subtype in distal ureter.

20 % of urinary tract stones are ureteral calculi and affect 5 – 10 % of the world population and majority of the patient are work force of society that belongs to 30 - 50 yrs of age group. So this disease has huge impact on socioeconomic aspect of society.[10] As per AUA alpha blocker is considered as first line treatment in ureteric calculus but its use is off label.[1] Alpha blocker known to increase stone free rate after ESWL (Extracorporeal Shock Wave Lithotripsy).[11] Although ureteroscopy has facilitated treatment and diagnosis of various urological diseases and it has given great success in stone disease management the surgical procedure has its own benefits.[6] Most of the complications occurs at the time of entry of ureteroscope in ureteric orifice. Many techniques have been suggested for reducing the complication while negotiating uretric orifice in order to decrease the complication, such as pre procedure dilatation has passive dialatation with help of insertion of DJ stent (double J stent), use of safety guidewire to exert lateral force on ureteric orifice to dilate ureteric orifice, active dilatation with help of balloon dilator, use of silastic gradual dilator. But these all are invasive techniques and majority of these techniques need anaesthesia to patient and we have to take patient in operation room, plus these techniques have their own complication rate.[12] Whereas alpha blocker is non-invasive safe drug with very low side effect and wide therapeutic window several RCTs(Randomised Controlled Trials) have shown good results with pre-operative use of alpha blocker for ease of ureteroscopy.[6]

The proposed hypothesis for use of alpha blocker for ease of ureteroscope is based on fact that stimulation of alpha receptor causes increased ureteric peristalsis, so selective alpha blocker of alpha 1A / 1D will cause relaxation and dilatation of uretric smooth muscle and cause dilatation / relaxation of ureteric orifice which will ease ureteroscopy and decrease complication rate.[13,14]

In study by Tan H et al,[6] metanalysis was done to see effect on alpha blocker on rate of complication. In this study perforation of ureter, false passage formation, bleeding was considered as complication. They found rate of complication is lower in alpha blocker group compared to placebo group ($p < 0.00001$) which shows use of alpha blocker before ureteroscopy lowers the rate of complication.[14]

The most critical point in the placement of ureteral access sheath is the passage through the ureter orifice and the intramural ureter section, which is the narrowest part of the ureter.[15] In a study by Erturhan S et al, alpha-blocker was used to relax ureteric orifice and intramural ureter section to facilitate placement of URS, it is seen that no statistically significant difference was noted in alpha-blocker

and patient without alpha-blocker group (65.2 % vs. 44 %; p = 0.141).

Use of alpha blocker in BPH patient is mainly to relax smooth muscle of prostate and which in turn decrease the bladder outlet obstruction and improve the flow of urine and prevent any complication which would arise due to increased BOO (Bladder Outlet Obstruction) such as AUR, bladder trabeculation, and damage to upper urinary tract. In prostate alpha 1a receptor are present in abundance and that is basis of use of selective alpha 1 a blocker such as tamsulosin, silodosin, alfuzosin. There isn't any study which would assess the relaxation of ureteric orifice in patient of BPH who are already on alpha blocker and planned for TURP (Trans-Urethral Resection of Prostate). For the very fact that these patients requiring operation despite on medical management shows that alpha blocker are not effective in preventing proposed mechanism of complication.[16]

We failed to find any study in the literature examining the effect of alpha-blocker on ureteric orifice in non-ureteric calculus patients showing or disproving its relaxing effects. So this study is an effort to find this relation and to look for possible relation of relaxation of the ureteric orifice to other factors. As our study demonstrates that alpha-blockers failed to show a statistically significant difference in relaxation of the ureteric orifice in non-ureteric calculus patients. Similarly to support our finding study by A. Sokhal et al[3] a prospective, case-control study on 124 patient of lower ureteric calculus with and without alpha-blocker group showed total 41 patients didn't need VUJ dilatation before insertion of ureteroscope, among them 16 (39.02 %) patients were from non-alpha blocker group and 25 (60.98 %) were from alpha-blocker group. This study doesn't show a statistically significant result (p value 0.57). The rate of complication among both groups didn't show any statistically significant difference p-value - 0.15).

CONCLUSIONS

Alpha-blockers failed to show a statistically significant difference in relaxation of the ureteric orifice in non-ureteric calculus patients, which is assessed by comparing ease of ureteroscopy and need of dilatation. May be alpha blocker isn't the only factor causing relaxation of ureteric orifice and some other factors need to be evaluated. Further large group, multi-centric studies are required to find a definitive role for alpha blockers prior to URS.

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