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ROLE OF ORAL THIOCOLCHICOSIDE AND ETORICOXIB IN MANAGEMENT OF MID AND LOWER URETERIC CALCULI WITH SEMI RIGID URETEROSCOPE.

Urology

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ABSTRACT

Objective: To evaluate the role of oral thiocolchicoside and etoricoxib in the management of mid and lower ureteric calculus with semirigid ureteroscope.

Material and methods: Between January 2017 and March 2018, 144 patients who presented with ureteral stone of size 8-12 mm were randomized into 4 groups: Group A- thiocolchicoside, Group B- etoricoxib, Group C- both the drugs and Group D - placebo. During surgery ureteral orifice appearance, requirement for ureteral dilatation, ureteroscope negotiation time, total operating time, procedural complication and drug related side effects were noted in each group.

Results: Significant number of cases in group A and C had wide orifice appearance and did not require dilatation as compared to placebo. Scope negotiation time through the orifice up to the stone was significantly lower in group A and C. In group B there was no statistically significant difference in the orifice appearance, requirement for dilatation and scope negotiation time as compared to placebo. Total operative time was also significantly lower in groups A and C ($p = .001$), but not in group B ($p = 0.315$) as compared to placebo.

Conclusion: Thiocolchicoside appeared as a safe and effective treatment to make ureteroscopy easy and reduced the total operating time plus the risk of complications. Etoricoxib did not have any beneficial effect during surgery. No major drug related side effects were observed in our study.

KEYWORDS

Thiocolchicoside, Etoricoxib , Ureter stone, Ureteroscope.

INTRODUCTION:

Ureteric stone disease is a common problem worldwide[1], with studies reporting incidence between 3% to 18% in various regions of the world [2]. Ureteroscopy by semi-rigid ureteroscope (URS) and laser lithotripsy is a commonly used procedure for treating ureteric calculi, however negotiation of URS through the ureteric orifice and the ureter may sometimes be very difficult as the uretero vesical junction is narrow, the ureter has a small calibre and ongoing inflammation can further worsen the situation**.**

It is reported that about 40-60% of the cases with ureteric calculus require dilatation of the ureteric orifice before negotiation of the ureteroscope [3]. Various drugs and techniques have been described to overcome difficult ureteroscopic negotiation but none of them is exempt from complications.

Bhattar et al [4] reported that the use of oral silodosin and tadalafil prior to surgery help in forward propagation of large size ureteroscope without any significant risk of adverse events. Akin et al [5] had reported that the use of injection thiocolchicoside in the irrigation solution used during surgery reduces the operative time and stone migration rates. Lodh B et al [6] reported that the administration of oral deflazacort prior to surgery significantly improved the outcome of ureteroscopy. Keeping this idea in mind we planned this prospective study to evaluate the role of orally administered thiocolchicoside alone plus its combination with etoricoxib in ease of performing surgery with semi rigid ureteroscope.

MATERIAL AND METHODS:

This prospective study was conducted in our department of Urology from January 2017 to March 2018 after taking ethical committee clearance. Patients from 18 to 55 years age with a diagnosis of single ureteric calculus of size between 8 mm to 12mm who underwent surgery with semirigid ureteroscopy under regional anaesthesia were included. Only patients with uncomplicated single ureteric calculus in the mid or lower ureter were included in this study.

Exclusion Criteria: Patients of age < 18 or > 55 years, surgery under general anaesthesia, ongoing urinary tract infection, acute or chronic renal insufficiency, multiple or bilateral ureteral stones, solitary kidney or congenital urinary tract abnormality or patient having history of any open ureteric surgery in past were excluded.

Patients with history of recent or ongoing treatment with steroids, alpha / beta-blockers, calcium channel antagonists or nitrate drugs, history of bleeding diathesis, patient's unwillingness for surgery, orthopedic or spinal deformity that restricted proper positioning, allergy to the study drugs, pregnant or lactating females and history of epilepsy were also excluded.

After written informed consent, patients fulfilling the above criteria were randomized in 4 groups by random number tables. Drugs used in the study were Thiocolchicoside, Etoricoxib and placebo in the following schedule. Group A- thiocolchicoside 8mg, 2 hours before surgery, group B – etoricoxib 120 mg – 2 doses , 1st dose one day before surgery & 2nd dose 2 hours before surgery, group C – both thiocolchicoside and etoricoxib as per schedule of group A and B respectively and group D - Placebo.

Demographic characteristics, height, weight were documented in all the groups. Serum creatinine, urine routine / microscopy, culture, ultrasonography, X-ray of the kidneys, ureters, and bladder, IVP or CT scan were done. Greatest dimension of the stone in any plane was considered as the stone size.

Surgical procedure: Semirigid ureteroscope of size 8 / 9.8 Fr (Richard Wolf GmBH, Germany) was used in all the cases. Cystoscopy was done with 19 Fr scope. Ureteric orifice was located and its configuration noted, 0.035 inch teflon guide wire was inserted. Ureteroscope was then inserted in the bladder and advanced into the orifice and ureter following the guide wire. If ureteroscope could not be negotiated easily then ureteric orifice dilatation was done with Nottingham dilator upto 10 Fr and then ureteroscope was passed. Ho:Yag laser was used for lithotripsy in all the cases. As a routine protocol of our institution double-J stent was inserted in all cases at the end of procedure. The surgery was performed by a senior urologist who was blind to the treatment groups.

Outcomes measured in the study: Ureteric orifice configuration, need or no need for ureteric orifice dilatation, total operating time, scope negotiation time (time taken to negotiate the orifice and reach upto the stone – if dilatation of the orifice was done then time taken to dilate was not included here) and procedural complications and side effects of the drugs were noted in each group.

Statistical analysis:

Data so collected was tabulated in an excel sheet and statistical analysis was performed with the SPSS for Windows. The Categorical data were presented as numbers (percentage) and were compared among groups using Chi Square test. The quantitative data were presented as mean and standard deviation and were compared using ANOVA Test and Post Hoc Test (Tukey Test) was applied to find out

the most significant group among all the groups. P value <0.05 was considered statistically significant.

RESULTS:

A total of 144 patients who met the study criteria were enrolled in the study and were randomized into 4 groups. The baseline preoperative characteristics of the study groups are presented in table number 1.

Table No. 1 – Baseline characteristics of the study groups.

Parameters	Group A (n= 35)	Group B (n= 36)	Group C (n= 35)	Group D (n= 38)	P value
Age (years) Mean ± SD	34.06 ± 9.33	37.44 ± 10.04	36.06 ± 8.47	38.16 ± 8.77	0.246 a
Male / Female (n)	20 / 15	19 / 17	19 / 16	21 / 17	0.986 b
Height (cms) Mean ± SD	163.2 ± 10.44	162.72 ± 10.54	164.09 ± 10.37	165.47 ± 10.57	0.69 a
Weight (kg) Mean ± SD	64.46 ± 8.51	65.61 ± 9.16	66.51 ± 8.10	65.05 ± 9.67	0.79 a
Stone Location (mid / lower ureter)	11 / 24	9 / 27	9 / 26	10 / 28	0.93 b
Stone size (mm) Mean ± SD	9.83 ± 1.29	9.92 ± 1.32	9.89 ± 1.49	10.03 ± 1.26	0.935 a

SD – Standard Deviation. a ANOVA (Analysis of Variance) , b Chi Square Test

Numbers of patients in Groups A, B, C and D were 35, 36, 35 and 38 respectively. There was no statistically significant difference among the 4 groups with respect to male: female ratio (p = 0.986), mean age (p = 0.246), mean height (p = 0.69), mean weight (p = 0.79) and stone location (mid / lower ureter, p = 0.93). Mean stone size in the 4 groups was 9.83 cm, 9.92 cm, 9.89 cm and 10.03 cm respectively with no statistically significant difference among the groups(p = 0.935).

Table 2 shows the comparison of the outcomes measured in the study groups.

Table 2. Treatment outcome parameters of the study groups.

Parameters		Group A (n= 35)	Group B (n= 36)	Group C (n= 35)	Group D (n= 38)	P value			
						A v/s D	B v/s D	C v/s D	A v/s C
Orifice Appearance	Wide	23/35	11/36	21/35	10/38	<.001	.68	.003	0.62[a]
	Narrow	12/35	25/36	14/35	28/38				
Ureteral Dilatation	Required	4/35	12/36	3/35	15/38	.006	.583	.002	0.69[a]
	Not Required	31/35	24/36	32/35	23/38				
Scope Negotiation Time (Sec.) Mean ± SD		18.71 ±8.14	29.36 ±9.07	19.63 ±8.30	30.13 ±6.61	.001	.89	.001	.89[b]
Total Operative Time (Min.) Mean ± SD		34.69 ±2.93	41.42 ±3.75	35.03 ±3.94	42.92 ±4.21	.001	.315	.001	.89[b]
Complications		4/35	14/36	3/35	16/38	.003	.778	.001	.69[b]

a Chi Square Test, b ANOVA with Post Hoc (Tukey) Test

Group A- Thiocolchicoside 8mg, 2 hours before surgery,
Group B – Etoricoxib 120 mg – 2 doses, 1st dose one day before surgery & 2nd dose 2 hours before surgery,
Group C – Both Thiocolchicoside and Etoricoxib as per schedule of group A and B respectively,
Group D - Placebo.

Significant number of cases in group A and C had wide orifice appearance as compared to placebo (p value A v/s D, C v/s D <.001 & .003 respectively), similarly requirement for ureteral dilatation was also significantly lower in group A and C as compared to placebo (p value A v/s D, C v/s D <.006 & .002 respectively).

Scope negotiation time through the orifice up to the stone was significantly lower in group A and C as compared to placebo (p value A v/s D, C v/s D - .001 & .001 respectively).

With respect to group B (etoricixib alone) there was no statistically significant difference in the orifice appearance (p value B v/s D- 0.68), requirement for dilatation (p value .583) and scope negotiation time (p value 0.89) as compared to placebo (group D).

Total operative time was also significantly lower in groups A and C (p = .001), but not in group B (p = 0.315) as compared to placebo.

As regards the complications pertaining to surgery like mucosal injury, hematuria, fever groups A and C had significantly lower incidence of complications (p value .03 and .001 respectively), while group B had similar complications as that of placebo (p value B v/s D – 0.778). None of the patients in the study experienced any drug related side effects.

DISCUSSION:

Urologists frequently encounter patients with ureteric calculus and manage them ureteroscopically in their day to day practice. However negotiating the ureteric orifice and reaching up to the stone is the most common problem which they face and is also the most common limiting factor for success of ureteroscopy.

Various techniques have been described to overcome this problem like active dilatation with balloons or passive dilatation with stents [7]. In the recent year's use of drugs like thiocolchicoside [5], deflazocort [6], silodosin, tadalafil [4] has been described to be useful during ureteroscopy.

Yigit Akin et al [5] had demonstrated the role of thiocolchicoside used in the irrigant solution during ureteroscopy and they concluded that locally administered thiocolchicoside significantly reduced the stone migration rates. Increasing the dose may also decrease operative time and use of double J stent.

Thiocolchicoside is a central muscle relaxant and has been used safely since long time by oral and parenteral routes [8]. Along with its muscle relaxant action it also has analgesic and anti-inflammatory properties [9]. It binds to GABA-A and strychnine sensitive glycine receptors and acts as GABA-A receptor antagonist, thereby producing relaxation of muscles [9]. Its myorelaxant effects are via complex regulatory actions and its action might be at the supra spinal levels [9].

In our study we used oral formulation of thiocolchicoside. Patients in thiocolchicoside groups had significantly lower ureteroscope negotiation time and total operative time as compared to placebo (p value .001) and majority of the cases had wide ureteric orifice plus significantly lower number of cases required orifice dilatation, suggesting that this drug had a beneficial role during ureteroscopy.

Kertmen et al had also reported relaxant effects of thiocolchicoside over the smooth muscles of brain vessels in a rabbit model [10]. They showed that cerebral vasospasm can be reduced by thiocolchicoside following subarachanoid haemorrhage. They concluded that GABA activity may play a role in cerebral vasospasm.

Around the ureter are peripheral branches of central nervous system and GABA receptors are located in these branches [11]. The relaxation produced by thiocolchicoside in the ureter can be due to the action over these receptors. Thiocolchicoside can connect to GABA receptors of peripheral neurons in ureter and the ureteric smooth muscle could relax due to it. However, definitive evidence for the same can only be found by molecular studies.

Lodh B et al [6] in their study showed that tablet deflazacort (a steroid) significantly improved the outcome of ureteroscopy under local anaesthesia. Corticosteroids are anti inflammatory agents; they stabilize neutrophil lysosomes and reduce inflammation and edema [12]. Selective cycloxygenase subtype-2 (COX-2) inhibitor non steroidal drugs (NSAIDs) have also been demonstrated to be effective in reducing ureteral contractility in animal and human ureteral segments in vitro [13]. Treatment with celecoxib (a selective COX 2 inhibitor) has also been shown to be useful in ureteric stone clearance [14].

In our study we used etoricoxib, which is a highly selective COX 2 inhibitor NSAID, and by inhibiting the enzyme cycloxygenase it reduces the production of proinflammatory prostaglandins and thus helps to reduce inflammation[15].

Our results of the etoricoxib group (group B) were not better than the placebo. The orifice appearance, requirement for orifice dilatation, total operative time and scope negotiation time in group B were comparable to placebo (group D) and the difference between groups B and D was not statistically significant (p value > 0.05).

In our study in group C we used both the drugs together i.e. thiocolchicoside plus etoricoxib, the results of this group C were significantly better than placebo (group D), but on comparison of this group with group A (thiocolchicoside alone), there was no significant difference (p value group A v/s C >0.05), means than the better results of group C as compared to placebo were due to the use of thiocolchicoside and not due to etoricoxib.

The lack of significant difference with etoricoxib in our study can be attributed to the short duration of treatment with this drug, etoricoxib has anti inflammatory actions but may be it requires long duration of treatment for these actions to produce significant effect.

The limitations of this study are that we have not done any molecular analysis, our study is purely based on observational data and also did not have any assessment of the normal anatomic (original) appearance of the orifice before drug treatment plus the assessment was subjective which can be a source of bias.

In conclusion, thiocolchicoside appeared a safe and effective treatment to make ureteroscopy easy and reduced the total operating time plus the risk of complications. Etoricoxib had no beneficial effect during ureteroscopy. No major drug related side effects were observed in our study. However further studies would be required to support our findings.

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