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C-reactive protein: A reliable parameter to predict the success of medical expulsive therapy using silodosin in small distal ureteric calculus

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Abstract

Background: Plasma C-Reactive Protein (CRP) is an acute-phase protein whose serum level increases in response to inflammation, as happens in impacted ureteric calculus. Few studies have investigated the efficacy of silodosin, a selective alpha 1-A adrenoceptor antagonist, in medical expulsive therapy (MET) for distal ureteral calculi. The studies showed the efficacy of silodosin 8 mg/day as a potential treatment for distal ureteric calculus expulsion. In this study wedetermined the correlation of CRP Levels at the starting of MET and the success of METwith SILODOSIN after 3 weeks.

Materials and Methods: 70 patients with distal ureteric calculus between 5-9 mm size were included in this study. They were divided into 2 groups based on the initial CRP level at the time of first presentation to the hospital.CRP level of 6mg/L was taken as cut-off.

Group 1 with 35 patients having CRP value morethan 6and Group 2 with 35 patients having CRP value of less than 6.

All patients were subjected to history taking, x-ray KUB, urinary tract ultrasound, non-contrast CT (CTKUB) scan and plasma CRP estimation. All patients received medical expulsive therapy with Silodosin 8mg per oral per day. All patients were advised to take oral diclofenac sodium 75mg/day for severe pain.

Patients were monitored on a weekly basis using ultrasound until spontaneous calculus passage or intervention, for 3 weeks.Number of renal colic episodes,analgesic usage and the time for stone expulsion were noted. Patients who failed to expel the calculus within 21days underwent ureteroscopy and stone removal.

Results: After 21 days, the groups were compared regarding the stone expulsion rate and duration for expulsion of stone, number of renal colic episodes and analgesic usage.

Median expulsion rates were 71.4% and 91.4% in groups 1 and 2, respectively and the difference between them was significant (P=0.031).

The median expulsion durations were 12.91±6.14 and 8.03±4.99 days, respectively and the difference between them was significant (P<0.001).

No significant differences were found regarding the median number of renal colic episodes or median analgesic dosage.

A cut-off point of 6.0 mg/L for CRP yielded appeared optimal for prediction of success of silodosin in medical expulsive therapy.

Conclusion: Medical expulsive therapy success for management of small distal ureteric calculi with oral Silodosin could be predicted with plasma CRP. Patients with CRP >6.0mg/L

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have low stone expulsion rate and failure of medical expulsive therapy and hence should directly be subjected for an immediate, minimally invasive ureteroscopy.

Keywords: CRP, distal ureteric calculus, silodosin, medical expulsive therapy

Introduction

The incidence of urolithiasis is estimated to be about 5-15% worldwide [1, 2] and incidence of symptomatic urolithiasis is increasing with changes in lifestyle and food habits.Ureteric calculus represent about 20% of the incidence and 70% of all ureteral stones are located in the distal ureter [3]. Although ureteral stones less than 10 mm in diameter spontaneously expulse in a significant percentage of patients without any intervention [2, 18], they can lead to serious problems without appropriate medical attention.

Stone size is the most important parameter to predict the possibility of the spontaneous passage and is one point to impress the patient upon the spontaneous passage or requirement for surgical intervention. The incidence of spontaneous passage of distal ureteric calculus 1 mm diameter was 87%, 2-4 mm 76%, 5-7 mm 60% and 7-9 mm 48% and more than 9 mm is less than 25% [1, 2]. Sometimes simple conservative management could lead on to complications, hence a need for a parameter to convince the patient regarding the need for intervention in order to avoid complications like urinary tract infections, recurrent colics and hydronephrosis and deterioration in renal function and urosepsis [3, 4, 5]. Serum C-reactive protein is a non-specific marker of systemic inflammation. C-Reactive Protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. It is an acute-phase protein. Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system [6].CRP is synthesised by the liver [6]. Because there are a large number of conditions that can increase CRP production, an elevated CRP level does not diagnose a specific disease. CRP has been proven to be useful in several clinical urological conditions such as estimation of renal injury in pyelonephritis[7], evaluation of the severity of urinary tract infection in children[7] and even avoiding voiding cystourethrography in children with febrile urinary tract infection and vesicoureteral reflux [7].

Lack of modern surgical instruments used in the treatment of ureteric calculiand complications with treatment options such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS) and open/laparoscopic ureterolithotomy have become concerns with the treatment of ureteral stones. These concerns,in addition to the high rate of spontaneous expulsion of ureteral stones have leadto the use of drug therapies that could facilitate stone clearance to become a primary consideration while treating patients with distal ureteric calculus.

Of the many drugs that have been tested for medical expulsive therapy (MET) in the treatment of ureteral stones, usage of alpha blockers have been validatedfor which sufficient data have been collected [19]. Alpha blockers are also recommended by the American Urological Association (AUA) and the European Association of Urology (EAU) for MET of distal ureteral stones less than 10 mm in diameter [17,18].

Alpha 1-A receptors are the most important adrenoreceptors for ureteral contraction [21]. Silodosin, which has greater specificity to alpha 1-A than other alpha blockers [19,20] is the latest alpha blocker approved for use.

The aim of our study is to assess the usefulness of CRP as abiochemical marker toassist in making a decision to subject the patients for medical expulsive therapy using Silodosinversus direct ureteroscopic interventionoflower ureteric stones.

Materials and Methods

The population of our study was composed of patients with distal ureteric calculi, size ranging from 5-9 mm.

Inclusion Criteria All male and female patients older than 18 years were eligible for inclusion in this study.

ISSN2515-8260 Volume 05,Issue 01,2018

Exclusion Criteria-Patients with urinary tract infection, severe hydronephrosis, multiple ureteral stones, pregnancy, solitary kidney, impaired renal function, associated ureteric anomaly, previous ureteric surgery or endoscopic procedures, painful symptoms experienced for more than 1 day and the patient's wish to remove the stone immediately. Patients suffering from any inflammatory disease (Viral infection, arthritis, gastroenteritis, hepatitis or respiratory infection), active neoplasia, cardiovascular disease (including hypertension), overweight/obesity, diabetes or liver failure are excluded from this study. Both inflammatory and neoplastic conditions may elevate CRP and conversely hepatic disease may lead to impaired CRP synthesis. Additionally, we exclude patients with history of certain medications as statins, steroids and oral contraceptives that affect CRP.

All eligible patients were informed about the opportunity to be recruited into the trial. Ureteroscopy was suggested as an alternative therapeutic option.

All patients were subjected to history taking, KUB, ultrasound and Non-Contrast CT (NC-CTKUB) scan to diagnose stone site and size. Non-Contrast CT (NC-CTKUB) scan is internationally accepted as gold standard for the investigation and measurement of ureteric calculi. CRP values checked only upon initial presentation along with the renal parameters (before use of diclofenac and other NSAIDs, as these drugs reduce CRP).

Serum CRP was measured by dilution method using a latex agglutination test, AVITEX CRP (Omega Diagnostics Ltd., Alloa, Scotland, UK). The method used was that described by the manufacturers. It was performed by mixing equal volumes of latex reagents with undiluted sera of patients. Normal CRP level in our laboratory is < 6 mg/L. Level above 6 mg/L were considered as high.

All patients received Silodosin once daily and they were allowed to use symptomatic therapy with oral diclofenac 75 mg (on demand). In addition, all subjects were instructed to drink 2 L of water daily. To observe possible stone expulsion, all patients were required to filter the urine.

Patients were invited to the clinic for weekly control visits to be questioned regarding any adverse effects related to medical therapy, stone expulsion, need for analgesics (i.e., dosage of diclofenac sodium being taken), and the number of renal colic episodes experienced recorded.

At these weekly visits the results of urinary system ultrasonography, complete urinary study, and blood chemistry regarding renal function were reviewed.

Patients who experienced stone passage were also invited for weekly control visits to record the passage duration and confirm passage of radiopaque stones by X-ray or radiolucent stones by low-dose unenhanced computed tomography.

All patients were examined weekly using USGKUBuntil spontaneous stone passage or intervention after 3 weeks. Patients who failed to expel the stone within 3 weeks underwent ureteroscopy.

Results

A total of 70 patients were included in the study.

Descriptive statistics were reported in terms of the number (n), percentage (%), median and range (minimum-maximum) of values. Fisher's exact test and Pearson's chi-squared test were performed for analysis of categorical data. Assumption of normality is controlled with the Shapiro-Wilk test. The Mann-Whitney U test was performed to compare the differences between the two groups. The Spearman correlation test was performed to determine the quantitative variants. All analyses were performed using SPSS version 18.0 (Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Review of the demographics of the two groups revealed that group 1 was 57.1% male and 42.9% female and of median age of 35.23±11.20 years and group 2 was 54.3% male and 45.7% female and of a median age of 35.31±11.55 years. No statistically significant differences were found between the two groups regarding sex or age (P>0.05; Table 1).

The stone size of the two groups ranged from 4 mm to 9 mm. The median stone size was

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6.40±1.61 mm in group 1 and 6.34±1.57 mm in group 2. No significant difference was found regarding the stone size between two groups (P>0.05).

Table 1: Review of the demographics of the two groups

	Group 1	Group 2	P
Sex[#] n (%) Male	20 (57.1%)	19 (54.3%)	0.810
Female	15 (42.9%)	16 (45.7%)	
Age[ǂ] (years)	35.23±11.20	35.31±11.55	0.953
Stone size[ǂ] (mm)	6.34±1.57	6.40±1.61	0.848

[#]Data analyzed with the Pearson chi-squared test.
[ǂ]Data analyzed with the Mann-Whitney U test.

Table 2: Stone expulsion duration, number of renal colic episodes, analgesic dosage and stone size

	Group 1	Group 2	P
Stone expulsion (+)[#] n (%)	10 (28.6)	3 (8.6)	0.031[*]
Stone expulsion (-)	25 (71.4)	32 (91.4)	
Stone expulsion duration (days)	12.91±6.14	8.03±4.99	<0.001[*]
Renal colic episodes[ǂ] (number)	1.49±1.48	1.17±1.44	0.266
Analgesic dosage[ǂ] (mg)	156.43±140.16	113.57±130.38	0.159

[#]Data analyzed with the Pearson chi-squared test.
[ǂ]Data analyzed with the Mann-Whitney U test.
[*]Significant difference.

The stone expulsion rate at the end of day 21 was 71.4% in group 1 and 91.4% in group 2. The difference between these rates was found to be statistically significant (P=0.031).

The median duration until stone expulsion was 12.91±6.14 days in group 1 and 8.03±4.99 days in group 2. The difference between these durations was found to be statistically significant (P<0.001).

The number of renal colic episodes was 1.49±1.48 in group 1 and 1.17±1.44 in group 2. The difference between these numbers was not found to be significant (P=0.266). The median dosage of diclofenac sodium usage was 156.43±140.16 mg in group 1 and 113.57±130.38 mg in group 2. The difference between these dosages was not found to be statistically significant.

Table 3: Associations among stone expulsion duration, number of renal colic episodes, analgesic dosage and stone size

		Stone expulsion duration	Number of renal colic episodes	Analgesic dosage	Stone size
Stone expulsion duration	P		<0.001[*]	<0.001[**]	0.001[**]
	r		0.476	0.439	0.389
Number of renal colic episodes	P			<0.001[**]	0.015[*]
	r			0.967	0.290
	P				0.032[*]
A[*]P<0.05; [**]P<0.01. Data analyzed with the Spearman correlation test. r values show the correlation coefficient	r				0.257

Discussion

Ureteral stones affect 15% of the population and are commonly diagnosed at emergency rooms[1] and urologists are frequently asked to choose an effective and safe therapy. Ureteroscopy represent the current mini-invasive therapeutic options for ureterolithiasis [5].

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Nevertheless, these procedures are not risk-free, are problematic and are quite expensive[2,3,4]. Observation of ureteral calculi, although attractive since it avoids invasive procedures is associated with pain, uncertainty, potential risks to renal function, urinary tract infection and occasionally loss of work. Therefore, it is difficult to choose between minimally invasive therapies and a watchful-waiting approach, especially when patients report few symptoms and/or stones are small[5,6]. Medical therapy with alpha blockers like Silodosinproved to induce stone expulsion and to relieve ureteral colic pain as shown by significantly less analgesic use, consequently determining the possibility of good home patient management and a loss of fewer working days. Recently others have observed that a conservative approach to ureteral stones is associated with lower cost compared with any invasive procedures (Ureteroscopy) only if it is successful that is followed by stone expulsion [8,9]. In fact, failure of conservative therapy results in higher costs than for first line ureteroscopy since it implies the loss of more working days as well as the need of a larger number of urgent urological visits. Patients who were not stone-free after the 3-week follow-up were successfully treated with ureteroscopy. These data demonstrate that neither watchful waiting nor medical therapy seems to negatively affect the success rate of stone removal [5,6]. The decision to proceed with intervention (Ureteroscopy) or to continue observation of small ureteral calculi is complex. Data suggests that stone size influences the spontaneous stone expulsion rate [5,8,9]. Patient factors that must be considered include degree of pain, narcotic requirements, work requirements, family commitments and personal preference. In this study, we correlated serum CRP levels in patients with ureteric stone as a new parameter to assist in making a decision concerning intervention versus observation.Serum CRP level is a nonspecific marker of systemic inflammation. It is protein synthesised mainly in the liver and its determination of serum CRP may reflect the intensity of the inflammatory or infectious process [8,14]. It has been shown that larger calculi particularly tend to provoke intense inflammatory changes in the ureteric wall and that submucosal oedema in proximity to a stone may worsen ureteric obstruction, heightening the risk of impaction and retention [10]. According to some studies, which investigate the role of CRP as a diagnostic marker in some urological diseases[6,7] and depending on the ureteric wall inflammation induced by ureteric stones [10], we evaluate serum CRP level in patients with ureteric stones as a factor that predicts the success of Silodosin Use as MET in addition to other factors as stone size, site and degree of hydronephrosis. In our study, we reported that a significant association between spontaneous ureteric stone expulsion and serum CRP level implying that inflammatory changes in the ureteric wall and that submucosal oedema in association with ureteric stone may play a role in failure of medical expulsive therapy using silodosin for expulsion of distalureteric stone [10]. We noticed that serum CRP is significantly higher in patients who failed to expel the stone within 3 weeks than in those with spontaneous stone expulsion within 3 weeks.

Most studies of administration of alpha blockers for MET have focused on treatment of stones in the distal ureter [3]. All data collected to date indicate that irreversible renal damage does not tend to occur with an incomplete obstruction for the first 4 weeks in the absence of an aggravating factor, such as urinary tract infection. Therefore, a logical approach in the absence of aggravating factors appears provision of MET only after the passage of 4 weeks [9,17]. To narrow the safety margin in our study, we provided MET after the passage of 3 weeks. The patient's age, sex and laterality did not differ between both groups. Stone size was comparable in both groups. Using ROC curve in our study, a cut-off point of 6.0 mg/L for CRP yielded, appeared optimal for prediction of spontaneous ureteric stone expulsion (sensitivity 78.6%, specificity 89.3%, positive predictive value 85.1% and negative predictive value 77.4%). We believe that CRP [15,16,17]could be added as one of the factors that the urologist must consider when recommending medical expulsive therapy with Silodosinto patients with ureteral calculi (e.g. stone location, size, degree of hydronephrosis, UTI and symptom severity [1,2,5,14]. We conclude that CRP status might predict the likelihood of stone passage without intervention, indeed larger prospective trials are required to validate this hypothesis and provide consideration with appropriate statistical analyses of the above-cited

potential confounders that alter CRP value. This is especially relevant as many, if not most, patients with urinary tract stones have one or more of the conditions above.

Conclusion

Medical expulsive therapy success with oral silodosin 8 mgfor management of small distal ureteric calculi could be predicted with serum CRP value. Patients with CRP > 6.0 mg/L have low stone expulsion rate and should directly be subjected for an immediate, minimally invasive ureteroscopy and extraction of the calculus.

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