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Predictive parameters for medical expulsive therapy in ureteral stones: a critical evaluation

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Abstract To evaluate the predictive value of some certain radiological as well as stone-related parameters for medical expulsive therapy (MET) success with an alpha blocker in ureteral stones. A total 129 patients receiving MET for 5 to 10 mm ureteral stones were evaluated. Patients were divided into two subgroups where MET was successful in 64 cases (49.61 %) and unsuccessful in 65 cases (50.39 %). Prior to management, stone size, location, position in the ureter, degree of hydronephrosis, diameter of ureteral lumen proximal to the stone, ureteral wall thickness along with patient's demographics including body mass index (BMI) values were evaluated and recorded. The possible predictive values of these parameters for stone expulsion (and stone expulsion time) were evaluated in a comparative manner between two groups. The overall mean patient age and stone size values were 38.02 ± 0.94 years and 40.31 ± 1.13 mm^2, respectively. Regarding the predictive values of these parameters for MET-success, while stone size and localization, degree of hydronephrosis, proximal ureteral diameter and ureteral wall thickness were found to be highly predictive for MET-success, patients age, BMI values and stone density had no predictive value on this aspect. Our findings indicated that some stone and anatomical factors may be used to predict the success of MET in an effective manner. With this approach unnecessary use of these drugs that may cause a delay for stone removal will be avoided and the possible adverse effects of obstruction as well as stone-related clinical symptoms could be minimized.

Keywords Ureteral stone · MET · Stone expulsion · Predictive parameter

Introduction

Urinary system stone disease is a worldwide common pathology and affects about 5 to 10 % of the population [1, 2]. Of all the calculi treated, stones in the ureter may cause obstruction and colic pain necessitating an immediate medical intervention both to relieve the distressing symptoms and accelerate stone expulsion [3]. Although the spontaneous passage of the stone (with or without specific measures and/or medication) is the main expectance, some stone (size, localization and composition) and patient-(degree of obstruction, symptoms and the anatomy of the urinary system) related parameters should be well assessed for an appropriate and efficient management plan [4–8]. Regarding the factors affecting spontaneous passage of the stone(s), size and localization are the most commonly evaluated parameters so far in the literature [4, 7]. While the published data indicate that 71 to 98 % of the stones sizing <5 mm may pass spontaneously, results of a well-conducted meta-analysis revealed that the spontaneous expulsion rates for stones sizing <5 and >5 mm were 68 and 47 %, respectively [9–11].

Taking the relatively lower chance of spontaneous passage and the well-known problems associated with ureteral calculi sizing >5 mm into account, medical expulsive therapy (MET) mainly with alpha blockers (Tamsulosin) has gained importance in recent years to increase spontaneous passage, decrease possible complications, need for invasive

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interventions and eventually relevant healthcare costs [12]. Furthermore, studies demonstrated that MET for ureteral stones can decrease the need for analgesics and the frequency of colic episodes requiring emergency department visits [13, 14].

Regarding the success rates of MET, Hollingsworth et al., did well evaluate the results obtained with the use of calcium channel and alpha blockers in nine randomized, controlled studies and they were able to demonstrate a 65 % more spontaneous passage chance in favor of MET [15]. However, unlike these findings some other studies published in this regard have failed to show the same success rates MET reported in these studies [6, 11]. This observation let us to look for some additional factors other than stone size and location to make a good prediction for the spontaneous passage rate of the stone(s) treated [4, 9].

Clinical use of such reliable predictive parameters may enable us to avoid the unnecessary use of these drugs for a certain period of time during which distressing symptoms and obstruction caused by the stone(s) may affect the quality of life and result in unestimated functional as well as morphological alterations in the upper urinary tract.

In this present prospective study, we aimed to evaluate the predictive value of some certain stone and patient-related factors for the success MET for ureteral stones.

Patients and methods

Between July 2013 and July 2014, a total of 129 adult patients (>18 years) with 5- to 10-mm single radio-opaque ureteral stones were included in to the study program. Patients with multiple stones, previous stone-related procedures, distal obstruction, stent placement, congenital anomalies, active urinary tract infection, pregnancy or renal insufficiency were all excluded. Additionally patients requiring urgent stone removal and/or auxiliary procedures were not included. While the stones located above the iliac vessels were defined as "upper ureteral calculi", lower ureteral stones were defined as the stones located below the these vessels [7].

Prior to the treatment, a detailed information regarding the use of Tamsulosin and related side effects were explained to all patients and a written informed consent was obtained. In addition to a detailed history and thorough uro-genital examination biochemical evaluation, urinalysis and urine culture–sensitivity tests were performed. The study protocol has been approved by ethics committee of the institution. Although a non-contrast computed tomography (NCCT) was performed in all cases, plain X-ray of the kidney, ureter and bladder (KUB), ultrasound and excretory urography were done when necessary. All patients with positive urine culture were treated by proper antibiotic regimen.

In addition to the age and gender, the body mass index (BMI) of all cases were noted and all radiologic possible predictive parameters have been derived by making calculations from the NCCT evaluation. In this regard, in addition to the size, location, position and Hounsfield unit (HU) of the stones, the ureteric wall thickness at the located stone site (UWT), diameter of the ureter proximal to the stone (PUD), presence and the degree of hydronephrosis were carefully assigned and recorded during NCCT evaluation.

To define positioning of the stone(s) in the ureter (transverse or longitudinal), largest stone diameter determined on the axial and coronal NCCT images were taken into account to make this decision. On the other hand, PUD was determined on one NCCT slice proximal to ureteral stone on axial images [7].

Following these assessments MET with Tamsulosin (0.4 mg once daily, in the morning after meal) was initiated in all cases. Patients were re-evaluated weekly during 4-week follow-up and stone-free status (SFR) were evaluated by performing KUB and sonography first and NCCT in patients with any suspicion of stone.

The possible predictive values of patient, stone and radiological parameters on the success of MET (stone expulsion rates) were analyzed. Data are presented as mean ± standard error of mean. Statistical significance analysis was performed using the unpaired *t*, Mann–Whitney, and Chi square tests, Pearson and Spearman correlation analyses using prism 5.0 (GraphPad Software, San Diego, CA) have been used to evaluate the significance correlation between subgroups. $p < 0.05$ was considered to be significant.

Results

Of the 129 patients evaluated (97 men and 32 women; M/F 3.03), while 66 cases had upper ureteral stones (51 %) 63 cases (49 %) had lower ureteral stones. 60 stones were located in the right (46.5 %) and 69 stones (53.5 %) were in the left ureter. Patient as well as stone-related characteristics along with the data for predictive parameters in the whole group are being summarized in Table 1. During 4-week period of MET application, although a total of 64 cases (49.61 %) passed the stone, in 65 cases (50.39 %) stones stayed in the ureter despite this therapy.

The overall evaluation of the predictive value of these parameters for SFR after 4 weeks revealed that although there was a significant correlation between stone expulsion rates and the stone size ($p < 0.0001$), degree of hydronephrosis ($p < 0.0001$), PUD ($p < 0.0001$) and UWT

Table 1 Comparative evaluation of patient and stone characteristics in groups

	Overall (*n*: 129)	MET-successful (*n*: 64)	MET-unsuccessful (*n*: 65)	*p**
Age (years)	38.02 ± 0.94 (18–74)	37.23 ± 1.30 (18–63)	38.78 ± 1.35 (21–74)	0.4095
BMI (kg/m^2)	25.36 ± 0.23 (19–33.8)	25.01 ± 0.31 (19–32.4)	25.71 ± 0.33 (20–33.8)	0.1200
Degree of hydronephrosis (Grade)	1.45 ± 0.64 (0–3)	0.98 ± 0.07 (0–2)	1.91 ± 0.07 (1–3)	**<0.0001**
HU	627.6 ± 20.72 (210–1250)	589.5 ± 26.67 (210–1077)	665.2 ± 31.16 (258–1250)	0.0677
Stone burden (mm^2)	40.31 ± 1.13 (20–80)	34.30 ± 0.89 (20–56)	46.23 ± 1.79 (25–80)	**<0.0001**
Proximal ureteral diameter (mm) (PUD)	7.85 ± 0.24 (2.4–18)	6.30 ± 0.24 (2.4–12.4)	9.39 ± 0.31 (5.2–18)	**<0.0001**
Ureteral wall thickness (mm) (UWT)	3.13 ± 0.09 (1.2–5.6)	2.88 ± 0.44 (1.2–4.2)	3.79 ± 0.39 (2.8–5.6)	**<0.0001**

Bold values indicate statistical significance ($p < 0.05$)

BMI body mass index, *HU* Hounsfield unit

* Unpaired *t* test

Table 2 Evaluation of MET-success with respect to gender and stone related factors

	Gender		Stone location		Laterality		Stone position in the ureter		
	Male	Female	Upper	Lower	Right	Left	Longitudinal	Horizontal	Spherical
MET-successful (*n*: 64)	52	12	26	38	32	32	35	4	25
MET-unsuccessful (*n*: 65)	45	20	40	25	28	37	31	12	22
*p**	0.1535		**0.0222**		0.4822		0.1093		

Bold values indicate statistical significance ($p < 0.05$)

MET medical expulsive therapy

* Fisher's exact test

($p < 0.0001$) no significant correlation was present between the age, gender and BMI of the cases (p: 0.4095) as well as the laterality and density of the stones treated (p: 0.067) (Tables 1, 2).

Evaluation of SFR based on stone location demonstrated that while 26 cases out of 66 (39.3 %) with upper ureteral stones passed the stones, 38 cases out of 63 (60.3 %) with lower ureteral stones passed them. These findings indicated the meaningful effect of MET for stone expulsion in lower ureteral calculi. Detailed evaluation of the data related with stone position showed that while of the 16 stones located in transverse position, only 4 (25 %) passed after MET; of the 66 stones located in a longitudinal position, 35 (53 %) did pass during the same period. More importantly, regarding the predictive values of the parameters in a subgroup based manner revealed that similar to the data obtained in whole group, while stone size, degree of hydronephrosis, PUD and particularly UWT were highly predictive, age as well as the BMI of the cases and the density of the treated stones were not found to predictive enough for stone expulsion rates after MET in both upper and lower ureteral calculi (Table 3).

Lastly, evaluation of stone expulsion time in a subgroup based manner showed that while the mean period was 14.76 ± 0.87 (5–26) days for lower ureteral stones, this value was 21.46 ± 0.91 (7–27) days for the stones in upper ureter along with an overall mean value of 17.48 ± 0.75 days in the whole group.

The evaluation of the correlation between the predictive parameters and stone expulsion time again demonstrated that UWT, PUD, stone size, location and the degree of hydronephrosis were helpful enough to predict time to stone expulsion.

Discussion

Regarding the management, while relatively smaller (<5 mm), uncomplicated and asymptomatic stones may pass spontaneously and followed in an expectant manner [11], larger stones causing obstruction, colic pain and infection will require active removal. However, it is well known that although minimally invasive and effective currently used endourological procedures are not risk-free and may be expensive to some extent.

Regarding the spontaneous passage of these calculi without any intervention [4, 11], Miller and Kane reported the time to stone-free status for stones <2, 2–4, and 4–6 mm as an average of 8.2, 12.2 and 22.1 days, respectively [16]. Additionally, European Association of Urology guidelines indicates observation as the initial approach for patients with controlled symptoms harboring ureteral stones

Table 3 Comparative evaluation of patient and stone characteristics in a stone location based manner

	Upper ureter			Lower ureter		
	MET-successful (*n*: 26)	MET-unsuccessful (*n*: 40)	*p**	MET-successful (*n*: 38)	MET-unsuccessful (*n*: 25)	*p**
Age (years)	37.92 ± 2.27 (19–62)	38.03 ± 1.56 (21–59)	0.8439	36.76 ± 1.56 (18–63)	40.00 ± 2.48 (22–74)	0.2788
BMI (kg/m^2)	25.04 ± 0.40 (21–29.4)	26.08 ± 0.40 (20–32.1)	0.0624	24.98 ± 0.44 (19–32.4)	25.13 ± 0.55 (20–33.8)	0.8376
Degree of hydronephrosis	0.96 ± 0.10 (0–2)	1.85 ± 0.09 (1–3)	**<0.0001**	1.00 ± 0.09 (0–2)	2.00 ± 0.11 (1–3)	**<0.0001**
HU	629.8 ± 37.45 (210–1029)	634.90 ± 41.07 (258–1250)	0.8133	561.9 ± 36.58 (210–1077)	713.5 ± 46.80 (278–1100)	**0.0139**
Stone burden (mm^2)	34.88 ± 1.51 (20–56)	45.90 ± 2.40 (25–80)	**0.0025**	33.89 ± 1.09 (24–49)	46.76 ± 2.67 (35–80)	**<0.0001**
Proximal ureteral diameter (mm) (PUD)	6.65 ± 0.43 (2.4–12.4)	9.51 ± 0.45 (5.2–18)	**<0.0001**	6.06 ± 0.28 (2.8–10.0)	9.19 ± 0.38 (6.2–13.3)	**<0.0001**
Ureteral wall thickness (mm) (UWT)	2.60 ± 1.13 (1.2–4.2)	3.87 ± 0.13 (2.8–5.6)	**<0.0001**	2.36 ± 0.10 (1.2–3.7)	3.68 ± 0.14 (2.8–5.6)	**<0.0001**

Bold values indicate statistical significance ($p < 0.05$)

BMI body mass index, *HU* Hounsfield unit

* Mann–Whitney test

<10 mm [9]. Taking the relatively lower rates of spontaneous passage along with associated problems in ureteral calculi sizing >5 mm and into account, MET mainly with alpha blockers has recently emerged as an alternative management option to increase the spontaneous passage rates, decrease the rate of complications as well as the need for invasive interventions and eventually decrease the healthcare costs [12].

Based on this somewhat established role of alpha blockers in the management of ureteral stones, although acceptable success rates with increased expulsion rates, reduced lost workdays, urological visits and most importantly stone removal procedures [5, 12, 15, 17] this approach was not found to show the same efficacy in relatively larger stones in some other trials reported in the literature [3, 8, 11]. This observation let us to consider the importance of the predictive factors other than the size and location of the stones which have been evaluated in the majority of the studies published [4].

Among the parameters evaluated so far on this aspect, although stone size and location were well studied [7] few studies have focused on stone position (craniocaudal stone diameter obtained by CT images), degree of hydronephrosis and proximal ureteral dilation as other certain possible parameters in predicting stone passage rates after MET. Additionally, no study so far evaluated the possible effect of ureteral wall thickness at the site of the stone as a predictive factor for final stone expulsion rates after MET.

Evaluation of our data both in the whole group as well as in a subgroup based manner demonstrated well that, while the age, gender, BMI of the cases and stone density had no significant predictive value on this aspect in addition to the stone size and location, degree of hydronephrosis, diameter of the ureter proximal to the stone as well as the thickness of ureteral wall at the stone site were found to be closely related with the final stone-free rates after MET. Our current data emphazise the importance of prediction of success with MET where careful assessment and use of such predictive parameters will give the urologist certain advantages. First of all, they will let us to avoid the unnecessary use of these drugs for a reasonable period of time during which the distressing symptoms as well as obstruction caused by the stones may affect the quality of life of the patient in whom the therapy seems to be unsuccessful. Second and may be the most important possible unestimated functional as well as morphological alterations in the upper urinary tract during this observation period might be avoided.

Our current study has some certain limitations: first the number of cases evaluated in this study might be small but in the light of the highly limited published data available in the literature, we believe that our current findings will contribute to a considerable extent. On the other hand, although

we accepted the successful state as the stone-free status of the cases regarding the distal migration of the proximally located stones, this condition may also be accepted as an additional advantage of this treatment.

Conclusions

Our findings indicate that prediction of the success obtained with MET might be possible by evaluating some certain predictive parameters with some advantages mentioned above. Degree of hydronephrosis, diameter of proximal ureter as well as the thickness of ureteral wall at the stone site seemed to be highly predictive on this aspect. However, we believe that further studies with larger series of patients are certainly needed to strengthen the predictive value of these parameters as well as to prepare nomograms for this aim.

Conflict of interest We have no conflict of interest.

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