

Original Article

Safety and effectiveness of medical expulsive therapy for ureteric stone in three tertiary Hospitals in Ethiopia

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Abstract

Background: Urinary tract stone disease is the most common pathology, with a global prevalence of 12%; 20% of them are located in the ureters, of which 70% are in the distal third of the ureters. Within 7 years of treatment, the recurrence rate reaches up to 55%. Medical expulsive therapy for ureteric stones is a non-invasive modality, and avoids complications related to other treatment options. The aim of the present study is to evaluate the safety and effectiveness of medical expulsive therapy for ureteric stone in Tikur Anbessa Specialized Hospital, Menilik II Referral Hospital and Yekatit 12 Hospital Medical College urology divisions.

Methods: Prospective longitudinal study was conducted among patients with ureteric stones in the three hospitals from March 1 to June 31, 2023. Convenient sampling technique was applied to select the study participants. Combination therapy was given randomly to the study participants. Data were collected using data collection tool and analyzed using SPSS version 27. Associations were evaluated using chi-square test adjusted odds ratios (AORs) with 95% confidence intervals (CIs). The results are presented using text, tables, and graphs.

Results: Sixty patients were included with mean age 35 ± 13.71 years and 78.7% of patients were between 20 and 50 years old. Forty-nine (81.7%) of the patients were treated with tamsulosin. Treatment success was 76.7% and confirmed by ultrasound and CT for 86.7% of the cases. Thirteen-point three percent of cases reported drug-related lightheadedness and dizziness. There was no worsening of the disease during treatment period. Higher success rate was noticed in early treatment initiation (AOR: 17.5; 95% CI: 2.2, 139.4). Stone expulsion rate was higher in patients with distal ureteric stones compared to proximal ureteric stones (AOR: 4.5; 95% CI: 1.01, 20.5). Complications were lower in combination therapy than single drug ($p = 0.001$).

Conclusion: Based on our findings, medical expulsive therapy is successful, safe and the only non-operative modality of treatment for ureteric stones, with high success in distal ureteric stones sized 5 – 10 mm.

Keywords: effectiveness, safety, ureteric stones, medical expulsive therapy

Introduction

The use of medication to aid with the transit of ureteral stones before surgical management is known as medical expulsive therapy (MET). Urolithiasis is the third most common urological disorder following urinary tract infections (UTIs) and prostatic diseases, accounting for up to 20% of urological admissions(1). Its prevalence has increased in the past few decades(2). About 55.7% of urological stone diseases are found in the lower urinary tract (3). Twenty percent of the detected stones are ureteral and nearly 70% of them are in the distal one-third of the ureter(4,5). More than 70% of stone disease affect people in the age range between 20 to 50 years(6).

The usual presenting symptom is ureteric colic, described as episodic severe flank pain from persistent contraction of ureteric smooth muscle as a kidney stone moves down the ureter into the bladder. It has also huge economical repercussion; annually it exceeds \$5 billion USD(7). Patients can typically be managed at home with analgesics in the hope of spontaneous stone passing following clinical assessment and stone localization by non-contrast computed tomography (CT) of the kidneys, ureters and bladder(8). Conservative techniques like watchful waiting (WW) or MET have become more popular, especially in patients up to grade 2 hydronephrosis(9).

The human ureter has three alpha-1 receptor subtypes (alpha 1a, 1b, and 1d). It has been demonstrated that alpha-1a and 1d antagonists improve the likelihood of stone passage because they reduce peristaltic contraction, raise intraluminal pressure and increase urine flow(10). MET is more effective and safe in pediatrics with ureteric stone which is a challenge by smaller anatomic make up for surgical intervention(11). So, MET, which comprises alpha-blocker medications, has gained popularity to increase the rate of spontaneous stone passage, shorten the expulsion period and

reduce the requirement for analgesics (12). Tamsulosin, an alpha antagonist, has been extensively researched and has been shown to play a role in facilitating stone expulsion(13). Silodosin has recently been found to be more effective in MET than tamsulosin (14,15,16). Other pharmacologic classes used in MET include calcium channel blockers, corticosteroids and PDE5 inhibitors. Success depends on a number of variables, including stone size, location and ureteral characteristics.

In addition, inflammation and edema in the vicinity of the stone impaction also play a significant role in preventing ureteral stone passage(17). Spontaneous expulsion rates have been reported to vary from 71% to 98% for distal ureteral stones smaller than 5 mm and from 25% to 53% for stones between 5 and 10 mm(18). The only Ca^{+2} channel blocker with superior results is nifedipine(19). The goal of administering steroids are for anti-oedemic effects and to promote evacuation. Corticosteroid combining with nifedipine can maximize the stone expulsion rate(20, 21). MET success rate is more than 92% for uncomplicated ureteric-stones-size up to 10 mm utilizing tamsulosin for up to 12 weeks. Especially in places with limited resources, this may have significant therapeutic and financial benefits by lowering the number of interventional procedure and complications (22).

A health care provider's advice can help to avoid symptoms from growing worse and the recurrence of ureteral stones. The size and location of the stone from ultrasound (US), KUB and CT scan will give healthcare provider a good idea as to whether the stone can pass or not (23). Drinking at least 2 to 3 liters of fluid per day can help to pass small ureteral stones with or without MET. The most common NSAIDs including aspirin, ibuprofen and naproxen, must be taken by physician order(24,25).

Complications of ureterolithiasis include ureter spasm, renal abscess, infected stones, CKD(26), blockage, ureteral scarring and stenosis.

MET is said to be an effective and safe modality of ureteric stone treatment. To date there is no research findings which show the efficacy and safety of MET for ureteric stones in Ethiopia. In this research, we evaluated the safety and efficacy of MET in three government hospitals in Addis Ababa, Ethiopia. We hope that the findings will be used as a resource for health care providers and decision-makers, as well as a baseline study for future research. Therefore, the study aimed at evaluation of the safety and effectiveness of MET for patients with ureteric stone size less than 10 mm in Tikur Anbesa Specialized Hospital, Menilik II Referral Hospital and Yekatit 12 Hospital Medical College urology division.

Methods and materials

Study area

The research was conducted in Tikur Anbesa Specialized Hospital (TASH), Minelic II Referral Hospital (MIIRH) and Yekatit 12 Hospital Medical College (Y12HMC) department of surgery urology division in Addis Ababa, Ethiopia. The two hospitals (MIIRH and Y12HMC) have collaboration with TASH urology division with good urological setup; the services are conducted by TASH urology residents, fellows and seniors jointly with urologists assigned in each hospital.

Study design and period

Institutional based prospective longitudinal study was conducted from March1, 2023 to June 31, 2023.

Population

All patients who presented with urological stone diseases in TASH, MIIRH and Y12HMC urology divisions during the research period comprised of the source population. All patients with ureteric stone, treated with MET in TASH, MIIRH and Y12HMC urology divisions in the study period were the study population.

Inclusion Criteria

All ureteric stone disease patients with stone size <10mm with normal renal function, no other surgical indication, and those who gave their consents to be enrolled in the study group for MET were included in the study.

Sample size

After collection of data for one week before data collection started, it was estimated to get 4 patients per week in all study hospitals. Within 4 months of the study period expected to get population of 64, calculated with the following formula: $n_0 = (Z^2pq)/d^2$ and applying the finite population correction formula $n = n_0/[1 + \{(n_0 - 1)/N\}]$, which gives $n=54.9$; where, n_0 = the uncorrected required sample size, n = the required sample size corrected for finite population size; N = the population size (64); p = the population proportion (0.5 in this case), $q = 1 - p$, z = the z -value at 95% CI, which is 1.96, and d = the margin of error taken to be 0.05. Taking 10% attrition which is 5.5, the final sample size (n) was 60.

Sampling technique

A convenient (none probability) sampling technique was used.

Study variables

Dependent variable

MET safety and effectiveness

Independent variables

Socio demographic variables: age, sex, marital status, occupation, educational status, and address.

Relevant clinical information: main complaint(s), duration of the illness, medication history, history of surgery, risks for stone formation, comorbid condition, stone size & location, urinary anatomical abnormalities, duration of improvement of treatment.

Data collection instrument

Data collection tool was prepared by reviewing different literatures related to MET for ureteric stone. The tool contained sociodemographic data, relevant clinical information, diagnostic aids, stone site and size, indications of drug treatment, types and effects of the drugs treatment (outcome, elapsed time to expelled and complications) and confirmatory investigations. The tool was prepared in English and patients were communicated by their mother's tongue.

Data collection procedure

Data collectors (residents and fellows) were selected from the three hospitals and were oriented on the data collection procedures. The patients with ureteric stone suitable for MET were enrolled and some patients were randomly treated with combination therapy. The patients were re-communicated after 6 weeks of initiation of MET with either face to face or on phone call, all confirmatory images were carefully interpreted and findings were collected and completed the data collection. Throughout the study period, the process was supervised by the principal investigator.

Data quality assurance

Based on the finding from the pretest, the data collection tools were revised, adopted and time needed for filling the data collection tool was

estimated. All ureteric stone patients who came to the three hospitals and fulfilled the inclusion criteria were included after the data collectors clarified to the patients about what to do on research site and the process was supervised.

Data processing and analysis

Data was entered, cleaned, and stored by using SPSS version 27 for analysis. Frequency and percentage were used to describe the findings. For quantitative data, mean and standard deviation were used. Crude and adjusted odds ratios were determined using bivariate and multivariate logistic regression to identify associated factors for safety and effectiveness of MET. Variables with p- value < 0.25 at bivariate were taken as eligible for multivariate analysis and the level of significance of association was determined at p- value <0.05.

Results

Sociodemographic characteristics of study participants

In this research, 60 ureteric stone patients were enrolled with 100% response rate out of 780 urologic stone patients in 3 hospitals with in the 4 months of the study period. Thirty-five (58.3%) of them were male. The smallest age was 14 year and the highest was 76 year old with mean of 35 ± 13.71 years, and 78.5% of the patients were 20 to 50-year-old. About 80% of patients were from Addis Ababa (AA), 65% of the study groups were married, and 82% of them were educated up to secondary school and above. Regarding their occupation, 32%, 33%, 15% and 20% were government employees, private business workers, house wives, and students, respectively (Table. 1).

Table 1: Sociodemographic characteristics of the cases with ureteric stone size < 10mm in Addis Ababa, 2023 (n=60).

Variables	Frequency	Percentage
Sex of respondents		
Male	35	58.3
Female	25	41.7
Age (in year) respondents		
14 -35	40	66.7
36 – 55	13	21.7
56 – 74	7	11.6
Marital Status		
Married	39	65
Single	21	35
Address		
In Addis Ababa	48	80
Out of Addis Ababa	12	20
Educational Status		
Primary school	11	18.3
Secondary & above	49	81.7
Occupation		
Government	19	31.3
Private	20	33.7
Housewife	9	15
Student	12	20

The clinical situations

Eighty-percent of the cases presented with flank pain alone and the remaining with an associated symptom. Duration of the illness was between 5 days to 6 months; 21.7% of the patients presented within 15 days of the illness. Seventy eight percent of the patients have no known comorbidity, whereas 3.3%, 8.3%, and 10% have diabetes miletus, hypertension & others (such as RVI and asthma), respectively. Forty-six (76.6%) of the cases presented after they had antipain treatment and 2(3.3%) of the cases had additional antibiotics treatment (Table 2).

Table 2: The clinical situations of cases with ureteric stone <10mm within 4 months in AA, 2023(n=60).

Variables	Frequency	Percentage
Duration of the illness		
≤ 15 days	13	21.7
> 15 days	47	78.3
Comorbidity		
Diabetics	2	3.3
Hypertension	5	8.3
Others (HIV and asthma)	6	10
No	47	78.4
Medication history before MET		
Anti-pain	41	68.3
Anti-pain and Antibiotics	2	3.3
More	5	8.3
No	12	20.1
Chief compliant(s)		
Flank pain	48	80
Flank pain and hematuria	4	6.7
Flank pain, hematuria, nausea & vomiting	8	13.3

HIV, human immunodeficiency virus; MET, medical expulsive therapy

Investigation findings

All cases had normal RFT and CBC profiles. No U/A result found for 71.6% of the cases. All of the patients had abdominal-pelvic US that showed grade 2 hydronephrosis. All of them were diagnosed with CT scan; 25%, 8.3%, 65% and 1.7% of patients had proximal, mid, distal, and more than one site of ureteric stone, respectively. Ninety-five percent of the cases had single ureteric stone where as 5% of patients had 2 ureteric stones. There were no anatomic abnormalities except 3.3% of patients had mal-rotated kidney. The size of the stone's ranged from 5 mm to 9.4 mm with mean of 6.51 mm,

and about 56.7% of the cases had less or equal to the average stone size (Table 3).

Table 3: The findings of investigation of patients with ureteric stone <10 mm (n=60)

Variables	Frequency	Percentage
RFT		
Normal	60	100
Urine Analysis		
Normal	7	11.7
Suggested infection	10	16.6
No result	43	71.7
CBC		
Normal	60	100
Serum potassium		
Normal	13	21.7
No result	47	78.3
Abdominal Ultrasound		
Hydronephrosis	60	100
CT scan findings		
<i>Site of the stone</i>		
Proximal	15	25
Mid	5	8.3
Distal	39	65
2 sites	1	1.7
<i>Size of stone (average 6.51)</i>		
≤6.51	34	56.7
>6.51	26	23.3
<i>Number of stones</i>		
Single	57	95
Two	3	5
<i>Anatomic findings</i>		
Normal	58	96.7
Mal-rotated kidney	2	3.3

Pharmacological managements and outcomes

Forty-nine (81.7%) of the patients were treated only with tamsulosin and 11(18.3%) of patients were managed with combined drugs (tamsulosin and prednisolone). Duration of the treatment ranged from 15 to 42 days; 70% of the cases were treated for 30 to 42 days. Seventy-six point

seven percent (76.7%) percent of the cases were treated successfully, proven by US and CT scan in 86.7% of the patients, 13.3% of the cases by combined parameters such as noticed stone passage, no hydronephrosis on ultrasonography and no evidence of stone on KUB. Sixteen point seven percent of patients noticed expelled stones. No worsening of clinical course was found during the course of the treatment. Seventy percent of patients became symptom-free within 15 days of treatment. Eight (13.3%) of the patients reported to have light-headedness and dizziness; otherwise no serious complications were observed (Table. 4).

Factors affecting success of medications

Gender and stone size did not show significant association with the success of medical management. Based on the duration of the illness, medical management was more effective in early presentation (AOR: 17.5; 95% CI: 2.2, 139; $p=0.007$). When stone is situated in the distal ureter, MET 4.9 times more effective (AOR: 4.9; 95% CI: 1.01, 20.5, $p=0.049$) than proximal situated stone. There were no better effect in combination therapies than monotherapy (AOR: 2.2; 95% CI: 0.04, 10.9; $p=0.32$) (Table 5).

Relations of drugs with complications and time of symptom improvement

Time of symptom improvement in relation to mono- or combination therapy shows early improvement in case of monotherapy (Chi-square = 15.4; $p=0.001$). Occurrence of complication in relation with only tamsulosin and tamsulosin with prednisolone treatment group showed less complication in combination treatment (Chi-square=15.4; $p=0.001$) (Table 6).

Table 4: Drug treatments & outcomes of patients with ureteric stone <10mm in Addis Ababa, 2023 (n=60)

Variables		Frequency	Percentage
Drugs	Tamsulosin	49	81.7
	Tamsulosin + Prednisolone	11	18.3
Outcomes	Successful	46	76.9
	Failed	14	23.3
Confirmatory investigation	US + KUB	6	10
	CT	2	3.3
	Both	52	86.7
Non contrast CT	Normal	40	66.7
	Ureteric stone	14	23.3
	Not done	6	10
US & KUB	Normal	43	71.7
	Hydronephrosis	16	26.6
	Hydronephrosis + ureteric stone	1	1.7
Duration of treatment	≤30 days	42	70
	>30 days	18	30
Time of expulsion for those noticed stone passage (8)	≤15 days	4	6.7
	>15 days	4	6.7
Noticed Passed stone	Yes	8	13.3
	No	52	86.7
Time of symptoms improvement	≤15	42	70
	>15	14	23.3
	No change	4	6.7
Worsening during treatment	No worsening	60	100
Drugs complications	No	52	86.7
	Lighted headedness & dizziness	8	13.3

Table 5: Factors associated with success of medications for patients with ureteric stones <10mm in 3 Hospitals, Addis Ababa, 2023 (n=60).

Values		Successful expulsion		COR,95%CI	AOR, 95%CI	P-Value
		Yes	No			
Sex	Male	28(80%)	7(20%)	1.56(.46,5.18)	4.98(.81,30.85)	0.081
	Female	18(72%)	7(28%)	1.0	1.0	
Site of the stone	Proximal	8(53%)	7(47%)	1.0	1.0	0.71
	Mid	8(80%)	1(20%)	3.5(.3,39.1)	1.5(.1,17.5)	
	Distal	34(85%)	6(15%)	4.9(1.3,18.8)	4.5(1.01,20.8)*	
Stone Size	≤6.51mm	27(79.4%)	7(20.6%)	1.7(.5,5.5)	1.4(.4,1.4)	0.65
	>6.51mm	18(69.2%)	8(20.8%)	1.0	1.0	
Drugs	Tamsulosine	41(83.7%)	8(16.3%)	4.2(1.1,17.4)	2.2(.04,10.9)	0.32
	Tamsulosine +	6(54.5%)	5(45.5%)	1.0	1.0	
	Prednsulone					
Duration of treatment	10 – 20 days	22(91.7%)	2(8.3%)	8.8(1.6,49.1)	17.5(2.2,139.1) *	0.007
	21 -30 days	14(77.8%)	4(22.2%)	3.1(.5,19.5)	6.1(.7,50.3)	0.08
	31 – 42 days	10(55.6%)	8(44.4%)	1.0	1.0	

Table 6: Relations of drugs with complications & time of symptoms improvements of management of ureteric stone <10mm, Addis Ababa, 2023(n=60).

Variables		Medications		Chi-square	P-value
		Tamsulosin	Tamsulosin+ prednisolone		
Time of symptom improvement	≤ 15 days	36(85.7%)	6(14.3%)	15.4	0.001
	>15 days	9(64.3%)	5(35.7%)		
Complications	Lighted headedness	7(87.5%)	1(12.5%)	15.4	0.001
	No	42(71.9%)	10(33.1%)		

Discussion

The aim of the study was to evaluate the effectiveness and safety of MET for ureteric stones, size < 1 cm. No similar studies have been done in Ethiopia. According to the source population, we found that there were 780 urological stone disease patients. The number of ureteric stone cases was expected to be 20% (4, 9) of 780; this means around 156 patients; some of the 156 may be excluded with exclusion criteria, but the expected study population could be higher than 60, so this data shows that MET in our country is underutilized. Seventy-eight point-five percent of patients were between 20 and 50 years old, similar to D'Costa's research, which was >70% (6). All of the cases presented with flank pain; 48 (79.9%) of the patients went to the nearby health institutions and took repeated anti-pain, and few of them took antibiotics, which could be the cause of the delay to initiate MET, which was 5 to 180 days of the onset of the illness.

Starting treatment early has a significant positive association with the stone expulsion effect of the drugs. Consistent with the principles, our study group had a normal RFT. All of them had grade 2 hydronephrosis (9). The number of patients treated with tamsulosin monotherapy was 49 (81.7%). Contrary to other studies, such as Bos' research, which reported success rates of 60% and 84.8% for tamsulosin and combination

therapy groups, respectively (17), our study found no better effect in expulsion success of combination therapy, which may be attributed to small number of patients and by chance most patients with proximal ureteric stones took combination therapy, who are at a higher risk of failed expulsion.

Forty-six (76.7%) of patients had successful stone expulsion, which is similar to most of the research findings but lower than the research done by Imperator et al., which found that 82% of the cases had successful expulsion (16). There was no relation between the size of the stone and expulsion; this can be explained by all the sizes of the stones being in the indication range of MET, and also its effect was influenced by the stone site, which was statistically significantly related; the distal ureteric stone had a 5 times higher probability of expulsion than the proximal ureteric stone (27).

Better symptom improvements in both medication groups were observed within 15 days of treatment. Our result, like many other studies done anywhere about MET, found it to be safe. There were no serious side effects of the drugs (28), except 13.3% of the cases claimed to have light headedness and dizziness higher than the other research result which is 3.2 to 4.2% (17). Relation of the complication with the drugs was

showed more complication in monotherapy groups.

Conclusion

METs are successful, safe and non-operative modality of management of ureteric stone, preferably for distal ureteric stone size 5mm up to 10mm. Starting the medications early within 15 to 20 days of the illness has excellent stone expulsion rate.

Acknowledgement

We would like to express our deepest gratitude first to the Almighty of God for giving us, health and protection. Secondly, to Addis Ababa University Tikur Anbesa Specialized Hospital (TAHS), Menilik II Referral Hospital, and Yekatit 12 Hospital Medical College urology division for providing us the opportunity to perform this research. We would also to thank our friends and seniors who helped us persistently in collection of appropriate data and giving enormous advice. We would also like to express our deepest gratitude to Dr Getabalew Endazene, Ato Ephrem Mamo, and Ato Yared Birhanu who gave us their precious time to read and comment the paper and for their enormous inputs in this paper. Genuinely, we got much help from W/o Syntayehu Abera and W/t Mareshet Amde who gave the questioners to the data collectors assigned at referral clinic every day during the data collection period without any interruption.

Ethical considerations

Ethical clearance obtained from the research review team of the TASH Surgical Department & the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University. Permission letters obtained from TASH surgical department, explained the aims

of the study for study participants. Information collected after obtaining verbal and written consent from each participant. For the purpose of anonymity, participants' names not mentioned at the time of data collection and confidentiality of all other personnel information was assured throughout the data collection process.

Data Availability statement

The data are available for anyone who wish to gain the access to the data upon request to the principal investigator via the following email: misganawtesfa2022@gmail.com.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding statement

Tikur Anbesa Specialized Hospital has funded the research. The funding institution had no part in the study design, information gathering, analysis, judgement to publish, or development of the manuscript.

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