

**Full Length Research Paper****Conservative Treatment versus Early Ureteroscopy in Obstructing Lower Ureteric Stone 6-10 mm: Multicenter Prospective Randomized Study**

Mohamed Naguib¹, Ahmed Ragab¹, M. Ali¹, K. Abdelwahab¹, Amr Fawzy¹, A sakr¹, A Eliewa,¹ Esam Shalaby², Mamdouh M ELHawy³, D.Elsaid¹, H.Desouky¹, M.Seleem¹, M Kamel¹, E. Desouky¹, M.Omran¹, H.Elgalaly¹, E.Salem¹, T. Dawod¹ M. Teleeb, Lotfy. B and A Shahein¹, A. Marouf¹.

¹Urology department, Zagazig University, Egypt.

²Urology departments, Suez Canal University, Egypt.

³Urology department, Menia University, Egypt.

Abstract

We performed multicenter prospective randomized study to determine the appropriate first line treatment modality for obstructing distal urethral stones (6-10 m). either medical expulsive therapy (MET) or ureteroscopy by comparing them safety and cost effectiveness. This prospective randomized study was done. On three thousand, one hundred and twenty four patients, one hundred and twenty four patients were withdrawn from the study, the remaining patients were randomized into two groups, group A (1500 patients were treated by MET using Silodosin 4mg for Maximum 28days) and group B (1500 patients were managed using semirigid ureteroscopy. At each visit during the follow up we evaluate the primary and secondary outcomes. The average stone size was 7.5mm (6-10). Success rate for Group A and B was 90.7% and 93.3% respectively. The average hospital stay in Group (B) was 60 hours while no hospitalization needed in Group (A). The overall complication rate was 25.4% and 14.2% In-group A and B respectively. The cost in-group (A) showed highly statistically significant Value <0.05 compared with Group (B). Conservative treatment MET takes the advantage of outpatient clinic treatment, non-invasive cost effective, with statistically insignificant different as regard the safety and efficacy.

Keywords: Distal urethral calculi, conservative treatment and Ureteroscopy.

Introduction

Urinary stones represent the third common disease of the urinary tract (Leslie, 2006). Segura and associates 1997 revealed that in distal urethral calculi (DUC) less than 5mm, the spontaneous passage rate ranges from 71% to 98%, but stones larger than 5mm had less passage rate. There is growing evidence that Medical expulsive therapy (MET) is effective in treatment of lower ureteric stones (Preminger et al 2007). Several studies have shown that alpha-blockers groups lower the time to stone passage, minimize patient pain and lower the need for analgesics. Yilmaz E. et al 2005). One of these groups is tamsulosin which was safe and effective that help spontaneous passage of distal ureteral stones sized 1 cm or smaller. Abdalla and colleagues' Parsons J, Hergan. With times ranged from 8 days to 6 weeks. Early intervention is required in cases with persistent obstruction, intractable pain, urosepsis and when the patients desire to be stone free for work or social related reasons (Porpiglia. Proponents of Ureteroscopy for distal ureteral stones, gives the high success rates, safety, low cost, low retreatment rates and widespread availability Ahmed and associates (TUGCU et al, 2006). We try in this study to determine the appropriate first line treatment modality for obstructing distal urethral stones (6-10 m).

Materials and Methods*Patient and methods*

From September 2013 to April 2015, 3000 Adult patients with a solitary distal ureteral stone that measures 6-10 mm were enrolled in this prospective randomized study, with exclusion of Moderate to marked hydronephrosis, Pregnancy, Previous lower ureteric surgery, previous stone expulsion, Persistent urinary tract infection and Stone in a solitary kidney after Informed patient consent they become 3000 patients.

They were randomized into two groups by (1:1) methods: group A (1500 patients were treated conservatively using Silodosin 4mg for 28 days) and group B (1500 patients were managed using semirigid Ureteroscopy)

Group (A) were managed in outpatient clinic in the form of: Silodosin 4mg /day, NSAIDS for pain (in severe attacks, strong pain-killer used e.g: opioids.), Plenty of fluid, up to four weeks and Antibiotic when needed. Follow up every week asking the patients to do; urine analysis, KUB, Abdominopelvic ultrasound and Non Contrast Spiral Computerized Tomography if needed. The End of conservative treatment was either by passage of the stone (1st outcome), or remarkable complication needs intervention; (sever agonizing pain or increase the back pressure), completion of 28 days of treatment and patients needs (2nd outcome). While in-group B: early intervention was done with semirigid Ureteroscopy 7-9.5f. Patients do routine preoperative workup if normal they were

admitted to the hospital and prophylactic antibiotic was given with the induction of anesthesia (third generation Cephalosporin). URS was done; guide wire was introduced; dilation of the ureteric orifice till 12f and Calculus was extracted using dormia basket (4wires) or stone forceps. An impacted stone was fragmented in situ using pneumatic Swiss® lithoclast. After termination of the procedure, inspection was done for the ureteric lumen for any residual or occult injury to assess if Ureteric stent was needed or not also we fix it in cases with in situ fragmentation, stone migration and difficult URS. All patients have been kept under observation in the hospital for hours which was differing according to the procedure. Postoperative antibiotics, symptomatic treatment and analgesia were given routinely Oral antibiotics (Ciprofloxacin 500 mg twice daily). After discharge, follow up by KUB radiogram was done before discharge and 2 weeks post-operatively to assess stone clearance. For complicated Patients every week for four weeks asking the patients to do; urinalysis, KUB, Abdominopelvic ultrasound, Non Contrast Spiral Computerized Tomography (NCST) to some cases.

Statistical analysis; used percentage, average, mean, chi square test and paired T Test using SPSS computerized program version 15.

Results

Our study was conducted on 3124 patients which fulfilled the criteria 103 patients refusing the procedure and refused to sign the consent and 21 patients who did not complete the study, they withdrew either due to drug adverse effect or lost during the follow up as shown in the flow chart (fig 1) the net results; Group (A) 1500 patients underwent conservative treatment and Group (B) early ureteroscopy was done, 1800 patients were males (60%) and 1200 were females (40%). The average age was 37.07 (26-55) years. Demographic distribution of both groups as shown in table (1) all findings are statistically insignificant P value >0.05.

Outcome and management

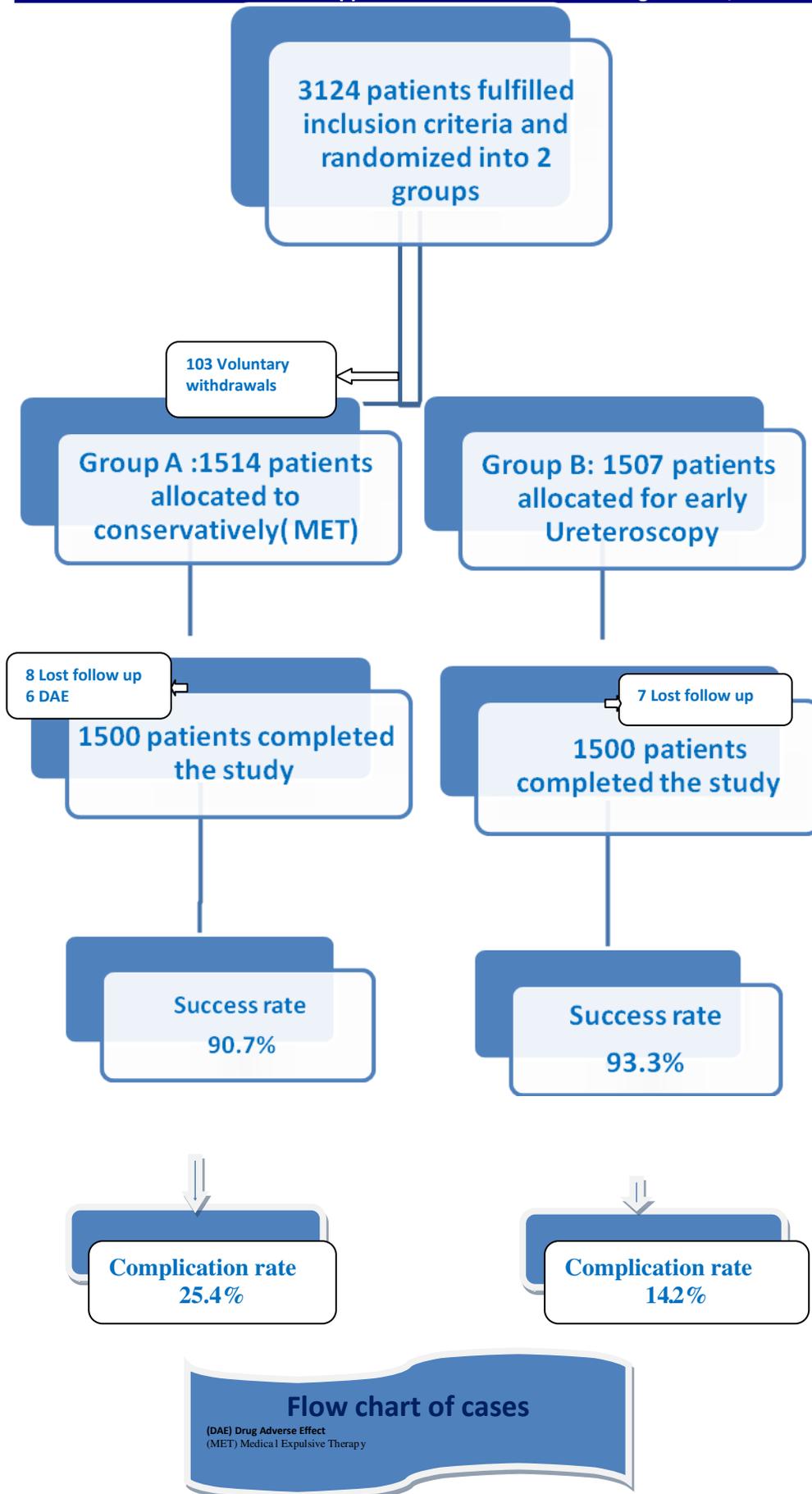
In-group (A); 1360 patients (90.7%) while 1400 patients (93.3%) in group (B) became stone free. In-group (A) only 140 patients failed for stone expulsion (9.3%) most of them due to the stone was transverse lie and impacted (123 patients). We shifted to ureteroscopy due to intractable pain in 100 patients and increase of the hydronephrosis at the end of the conservative period in 40 patients. The average treatment times were 13 (7-28) days. During the first two weeks most of stones size ranged from 6-8 mm were expelled while stone size from 8-10 mm persists to the last two weeks, also stones which were transverse lie in the ureter (197 patients) and impacted takes longer time to be expelled and a lot of them were shifted to URS (123 patients). In-group (B) the average operative time was 39.7 (35-46) minutes. Stones were retrieved by dormia basket in (60%) of patients, by stone forceps in (25.2%) of patients, were fragmented in situ by lithoclast in (13.3%) and DJ stent was fixed, the stone was migrated to the kidney in 25 patients (1.5%) and DJ stent was fixed. ESWL was done for 20 and the other 5 patients, stone was redescended again to the lower ureter during the follow up and were treated by URS when we remove the DJ. The average fluoroscopy time was 2.52 (2-4.3) minutes.

Table 1: Demographic of both groups:

Items	Group(A) N=1500	Group(B) =1500	P value
Mean age	36.5±13.8	36.8±9.1	>0.05
Sex:			
Male	780(52%)	820(54.7%)	>0.05
Female	720(48%)	680(45.3%)	>0.05
Radiological finding: laterality:			
RT	980(65.3%)	760(50.7%)	>0.05
LT	520(34.7%)	740(49.3%)	>0.05
Size: Mean (mm)			
Presentation	7.4mm±1.2	7.6mm±1.6	>0.05
Renal colic only	560(37.3%)	460(24%)	>0.05
Renal colic with hematuria	360(24%)	400(22.7%)	>0.05
Renal colic with LUTs	580(38.7%)	640(42.7%)	>0.05
Urine analysis findings			
Sterile urine	1200(80%)	1160(77.3%)	>0.05
Pyuria	300(20%)	340(22.7%)	>0.05

Complication in both groups

Group (A), Persistent renal colic was encountered in (6.6%) 100 patients (26 (1.7%) with fever, 37 (2.4%) with Hematuria) with temporary relief by opioids while the fever with persistent renal colic was managed by IV antibiotics and shifted to ureteroscopy, hematuria was stopped spontaneously, but failed to expel the stone, and shifted to Ureteroscopy. Retrograde ejaculation was occurred in 320 patients (21.3%) relieved after temporary stoppage of Silodosin, 3 patients (0.06%) with Epididymo-orchitis which was relieved by analgesics and antibiotic but complete resolution was done after stone passage all these types of complication were ranged from G1-2 by Procedure-related complication Category¹ Martin RC 2nd, Brennan.



While in- Group (B); false passages was occurred in 93 patients (6.2%) were managed by ureteral stent (DJ) for (12-30) days, Postoperative complications: Fever lasting for two days was encountered post URS in 60 patients. Hematuria occurred in 40 patients, Epididmoorchitis was encountered in 20 patients. All those patients were managed conservatively except 4 patients with Sever Epididmoorchitis need to hospitalize for 48-96 hours. All this types of complication was ranged from G2-3 by clavien scoring.² Dindo D, Demartines N, Clavien PA. the complication was insignificantly increased in Group (A) but mostly self cure rather than the complication of Group (B) which need auxiliary maneuver and prolonged hospital stay.

Table 2: Complications

Item	Group A	Group B treatment	X ² FISHER EXACT	
False passage	--	93 (6.2%)		NS
Retrograde ejaculation	320(21.3%)	--		NS
Fever	26 (1.7%)	60 (4%)		NS
Hematuria	37(2.4%)	40 (2.7%)	1.6	NS
Epididmoorchitis	3 (0.006%)	20 (1.3)		NS
Total	369 (25.4%)	253(14.2%)		

Failed treatment in Group A was 140 (9.33%) while in Group B Was 100 (6.66%) which was 0.6 NS. Average Post-operative hospital stay was 8-12h, uncomplicated cases, 72-96 h. in complicated cases in group (B). The mean monthly cost of the group (A) mainly the cost of Silodosin about 418.20±105.78 L.E. including cost of follow up. While the mean cost in group (B) was 2748.55±421.00 LE. This cost difference shows highly statistically significant where P value < 0.05.

Discussion

Stone diseases were the commonest problems in urology. (Stamateloueta /2003).The benefits for MET in many studies such decrease time for stone passage and decrease pain episodes.(YilmazEeta/2005).Our result agreed with most of the studies as regard the absence of association between age ,sex of the patient side of stone and nature of the treatment outcome (kanao etal2006)(Abdulla and colleagues). There was Meta- analysis study show that MET (alpha-blocker) enhance stone expulsion in about 81 % of cases. (AU AguidelinesfJ07).This result was similar to the result of Abdulla and collages Stone expulsion occurred in 41 of patients 50 82%) Also (NigroF and associate2007) conservative treatment for DUC less than or equal 1cm show success rate about 75%. However, our result was higher 90.7% may be due to the variety in inclusion criteria also the different in the type of alpha-blocker. Many other studies done on different types of MET, they differ in the treatment regimen and number of patients. Taghavi Retal, 2006 found that alpha-blockers success rate were 90%.which was similar to our result. The expulsion time was significantly shorter in the tamsulosin group (6.4±2.77days by Abdulla and colleagues while in our group 13(7-28) days which was prolonged as the previous study included stones less than 0.6cm and we used Silodosin. Meta-analysis study done to show stone free rate in URS in DUC ≤ 10 mm was about 94% (AUAguidelines2007).which was like to our result. The cost of alpha-blockers ranged from 10.74 \$ for 28-day doxazosin to 104.4 for 42-day tamsolusion course as based on drug-cost data obtained from university of Michigan pharmacy, the only non-generic medication.(Shuster TG and colleagues 2006) However, less cost than URS group. In this study patient received medical therapy was hospitalized, so the cost of URS and conservative treatment near each other, while in our-study without Met was taken without hospitalization. So the different in cost between URS and medical treatment is significant P value 0.00. (Nigro F.,et al 2007). But our cost was 98 L.E 28 days course of Silodosin. When conservative treatment succeeded, intervention is unnecessary.This advantage is important as the risks related of surgical intervention are not trivial (Shuster T G et al 2001). Shuster TG and colleges reported overall complication rates after URS of 10-20% with major complications occur in 3-5% of procedures. While in our study, overall complication rate was 14.2%, which was slightly similar. While in conservative treatment complication rate was 25.4%. According to our results conservative treatment offers non invasiveness and low grad complication rate than URS.

Conclusion

Conservative treatment takes the advantage of outpatient clinic,non-invasive, low cost and low grad complication than URS which was more effective than MET but need hospitalization, low incidence of complication but with high grad one. its first of choice when there was impacted or transverse lie of the stone. So we were starting to innovate nomogram for helping to choice the best modality for treatment from the start.

Reference

- Abdulla Al-Ansari, Abdulla Al-Naimi, Abdulkader Alobaidy, Khalid Assadiq, Mohamed D Azmi, Ahmed A Shokeir Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology 01/2010; 75(1):4-7.
- Ahmed R El-Nahas, Nasr A El-Tabey, Ibrahim Eraky, Ahmed M Shoma, Ahmed S El-Hefnawy, Ahmed M El-Assmy, Shady Soliman, Ramy F Youssef, Mahmoud R El-Kenawy, Ahmed A Shokeir, Hamdy A El-Kappany Semirigid ureteroscopy for ureteral stones: a multivariate analysis of unfavorable results. Journal of urology 02/2009; 181(3):1158-62.
- AUA guidelines 2007. Ureteral Calculi Management of Ureteral Calculi: EAU/AUA Nephrolithiasis Panel Copyright © 2007 American Urological Association Education and Research, Inc. ® and European Association of Urolog 2007 | Reviewed and validity confirmed 2010http://www.auanet.org/common/pdf/education/clinical-guidance/Ureteral-Calculi.pdf
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336

patients and results of a survey. *Ann Surg* 2004; 240: 205-13.

Keshvari M. Survey of the effect of tamsulosin and nifedipine on facilitating juxtavesical ureteral stone passage. *J Endourol* 2005; 19 (suppl 1): A9.

Leslie S and Savitz G (2006): The kidney stones management. *BMJ* 315: 53-63

Martin RC, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg.* 2002;235:803–813

Nigro F., Benedetto G., Ferrarese P., Abatangelo G., Scremin E., Bratti E., Tasca A. Ureteroscopy vs. conservative treatment of distal ureteral calculi San Bortolo Hospital, Urology, Vicenza, Italy *Eur Urol Suppl* 2007;6(2):270

Preminger G, Tiselius H, Assimos D, et al (2007): 2007 Guideline for the Management of Ureteral Calculi. *J Urol* 178: 2418-2434.

Porpiglia F, Vaccino D, Billia M, et al (2006): Corticosteroids and tamsulosin in the medical expulsive therapy of symptomatic distal ureter stones: single drug or association? *EurUrol* 50: 339-344

Schuster TG, Hollenbeck BK, Faerber GJ, Wolf JSJ. Complications of ureteroscopy: analysis of predictive factors. *J Urol* 2001; 166:538–40

Schuster T, Hollenbeck B, Faerber G, et al (2001): Complications of ureteroscopy: analysis of predictive factors. *J Urol* 166: 538-40

Segura J, Preminger G, Assimos D, et al (1997): Ureteral stones clinical guidelines panel summary report on the management of ureteral calculi. *J Urol* 158:1915-1921

Stamatelou K, Francis M, Jones C et al (2003): Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int* 63:1817-23.

Tugcu V, M.D, Gokhan G, Aras B, Gurkan A, et al., (2006): Primary Ureteroscopy for distal-ureteral stones compared with ureteroscopy after failed extracorporeal lithotripsy *journal of endourology* Vol; 20,.12., 1026; 1031.

Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. *J Urol* 2005; 173 *Pages 2010-2012*

Parsons J, Hergan L, Sakamoto K, et al (2007): Efficacy of alpha-blockers for the treatment of ureteral stones. *J Urol* 177: 983