Original Article

A comparison of stone free rate between a diuretic and a control group of patients undergoing extracorporeal shock wave lithotripsy: a prospective, randomized, double-blind, placebo-controlled trial

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Keywords:
Extracorporeal shock wave lithotripsy, diuretic, stone free rate

Abstract

Objectives: To compare the stone free rate and treatment success rate between a diuretic group of patients undergoing extracorporeal shock wave lithotripsy (ESWL) and a control placebo group (normal saline solution).

Materials and Methods: One hundred and ninety-four patients with solitary renal calculi or ureteric calculi size of 5 mm or over were prospectively randomized into 2 groups. Ninety-seven patients in the first group (diuretic group) underwent ESWL after intravenous injection of furosemide 40 mg, and 97 patients in the second (control) group received normal saline solution 4 ml instead of furosemide prior to ESWL. The treatment protocol included 3,000 shockwaves per patient in each session with the energy beginning at 8 and progressing up to 15 kilovolts. A maximum of 3 ESWL sessions were permitted per patient. The primary outcome was stone free rate, and the secondary outcome was treatment success rate at 3 months after the first ESWL treatment.

Results: The stone free rate was 48.5% compared to 50.5% for diuretic group and control group respectively and the treatment success rate was 81.4% compared to 64.9%. The difference in stone free rate was not statistically significantly different ($p = 0.87$), however the treatment success was, $p = 0.01$.

Conclusion: A combination of diuretic therapy followed by ESWL improves the treatment success rate compared with standard ESWL therapy alone.

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) has been used as a treatment of urolithiasis since 1980.[1] As a minimally invasive procedure, the efficacy of ESWL[2] is accepted worldwide especially in the treatment of small renal or ureteric calculi. However, some patients require repeat ESWL treatment due to the failure or limitation of stone fragmentation. The success of ESWL treatment depends on several factors including stone size, stone number, stone composition, and renal function.

Diuretics increase urine flow around the stone during ESWL,[3,4] therefore, improving stone fragmentation[5] and removal. The main mechanism employed is the cavitation phenomenon. When a shock wave generated by an extracorporeal shock wave lithotripter interacts with a solid, it can produce cavitation bubbles at the interface between the solid and the surrounding liquid. The implosion of the cavitation bubbles plays an important role in the disintegration of the stone.

The aim of this study was to compare stone free rate[6,7] and treatment success rate between a diuretic with ESWL and placebo (normal saline solution) with ESWL. The hypothesis is that the diuretic combined with ESWL improves the stone free rate and the treatment success rate when compared with standard ESWL therapy alone.

Materials and Methods

A prospective, randomized, double blinded, placebo-controlled trial was conducted between December 2020 and May 2021 at Chaophraya Yommarat Hospital. This study was approved by the Ethics Committee of Human Research (ECID: YM 033/2563) and approved by the Thai Clinical Trials Registry (TCTR) committee on 1st June 2021. The TCTR identification number is TCTR 20210601002.

From the original cohort of 200 patients, 6 patients were excluded due to loss of follow up, the remaining 194 patients were enrolled in the study. All patients had solitary radiopaque renal or ureteric calculi, written consent was given by all participants.

Demographic data including age, sex, body mass index (BMI), stone size, and stone location were collected. As shown in Table 1, the patients were randomly divided into 2 groups using computer-generated numbers. In the first group (diuretic group), the patients received 40 mg of furosemide intravenous injection 30 minutes before each ESWL session. In the second (control group), the patients received 4 ml of normal saline solution as placebo instead of furosemide 30 minutes before each ESWL session. All patients in both groups received hydration with normal saline 500 ml intravenously during the procedure at the rate of 60 ml/hour. Blood pressure, and oxygen saturation were monitored during the procedure. For ESWL, all patients were treated as outpatients under intravenous analgesia; pethidine 25 mg.

A Dornier Delta III (Dornier Medtech, Munich, Germany) machine was used for the ESWL, with 3,000 shock waves given at the rate of 60-90 shockwaves/minute with the energy beginning at 8 and progressing up to 15 kilovolts. Patients were followed up at the outpatient department every 3 weeks after ESWL for 3 months with a plain film kidney ureter bladder (KUB) x-ray.

ESWL was repeated if no stone fragmentation occurred or residual stone fragments were larger or equal to 5 mm. Patients were permitted a maximum of 3 sessions of ESWL, 3 weeks apart.

The primary outcome was stone free rate at 3 months after ESWL. Stone free rate was defined as the complete clearance of stone or no visible stone seen on plain film KUB. Clinically insignificant residual fragments (CIRF) was defined as residual fragments of stone smaller 4 mm or less on plain film KUB.

The secondary outcome was the treatment success rate, defined as the complete clearance of stone (stone free) or CIRF, and treatment failure was defined as having residual stone fragments over 5 mm on plain film KUB after 3 ESWL sessions.

Inclusion criteria were patients above 18 years old, with a single radiopaque renal or ureteric calculi size over or equal to 5 mm. The exclusion criteria were patients who were pregnant, suffered from uncontrolled coagulopathy, or urinary tract infection, and those with multiple or bilateral stones.

Statistical analysis was done using a statistical package for the social sciences (SPSS version 16; SPSS Inc: IBM corp., Armonk, NY, USA). Categorial variables were compared using the Chi-square test. Continuous data are presented as mean and standard deviation (SD), which were compared using a student's T test.

Results

A total of 194 patients were enrolled onto the study and randomly divided into two groups, 97 patients being allocated into each arm. There were no differences between the 2 groups with regard to age, sex, BMI, stone size and stone location (Table 1). The mean ages of the diuretic group and the control group were 54.23 years (SD 11.4) and 54.35 years (SD 13.5) respectively, p-value 0.95. The mean BMI of the diuretic group and the control group were 25.53 kg/m^2 (SD 4.93) and 25.23kg/m^2 (SD 3.83) respectively, p = 0.64. The mean size of the stones of the diuretic group and the control group were 9.63 mm (SD 4.65) and 10.27 mm (SD 4.59) respectively, p = 0.67. 108 patients (55.7%) had a renal stone and 86 patients (44.3%) had a ureteric stone. Patients with renal stones in the diuretic group and control group numbered 53 patients (49.1%) and 55 patients (50.9%) respectively. Patients with ureteric stone in the diuretic group and the control group totaled 44 patients (51.2%) and 42 patients (48.8%) respectively.

There was no statistical difference in the stone free rate of the diuretic group and the control group (48.5% vs 50.5%, p = 0.87). However, the CIRF incidence in the diuretic group was statistically significantly higher than in the control group (33% vs 15.5%, p < 0.01). In addition, the overall treatment success rate in the diuretic group was significantly higher than in the control group. (81.4% vs 64.9%, p = 0.01) Table 2.

There were 9 patients (9.3%) in the diuretic group and 11 patients (11.3%) in the control group respectively who received double-J stent placement due to steinstrasse and severe pain after ESWL. Three patients (3.1%) from both the diuretic group and the control group were treated

Table 1. Demographic data

Characteristics	Diuretic group (N=97) n (%)	Control group (N=97) n (%)	P-value
Sex			0.67
Male	51 (52.6)	48 (49.5)	
Female	46 (47.4)	49 (50.5)	
Age (years)			0.81
< 40	11 (11.3)	14 (14.4)	
41-60	55 (56.7)	53 (54.6)	
> 60	31 (32)	30 (30.9)	
Mean (SD)	54.2 (11.4)	54.4 (13.5)	0.95
BMI (kg/m^2)			0.35
< 18.5	4 (4.1)	5 (5.2)	
18.5-22.9	24 (24.7)	20 (20.6)	
23-24.9	24 (24.7)	16 (16.5)	
> 25	45 (46.4)	56 (57.7)	
Mean (SD)	25.5 (4.9)	25.2 (3.8)	0.64
Stone size (cm)			0.25
< 1	66 (68)	55 (56.7)	
1.1-2.0	28 (28.9)	39 (40.2)	
> 2.0	3 (3.1)	3 (3.1)	
Mean (SD)	9.6 (4.7)	10.3 (4.6)	0.67
Stone location			
Renal calculi (n=108)	53 (54.6)	55 (56.7)	0.73
Upper calyx	13 (13.4)	9 (9.3)	
Middle calyx	17 (17.5)	18 (18.6)	
Lower calyx	23 (23.7)	28 (28.9)	
Ureteric calculi (n=86)	44 (45.4)	42 (43.3)	0.47
Upper	24 (24.7)	25 (25.8)	
Middle	2 (2.1)	5 (5.2)	
Distal	18 (18.6)	12 (12.4)	

BMI = body mass index, SD = standard deviation

Table 2. Results of the ESWL treatment

Characteristics	Diuretic group n (%)	Control group n (%)	P-value
Stone free	47 (48.5)	48 (50.5)	0.87
CIRF[a]	32 (33.0)	15 (15.5)	< 0.01
Treatment success[b]	79 (81.4)	63 (64.9)	0.01

[a]Clinically Insignificant Residual Fragment, residual stone fragment less than or equal to 4 mm after 3 sessions of ESWL

[b]Treatment success; defined as stone free including CIRF

with Ureterorenoscopy to remove residual stones, 1 patient (1.03%) in the diuretic group and 3 patients (3.1%) in the control group required open stone surgery after failed ESWL treatment (Table 3). None of the auxiliary treatments showed any significant difference.

Discussion

ESWL is the treatment of choice for urolithiasis with small size stone, due to the minimally invasive nature of the procedure. The mechanisms involved[8,9] in ESWL treatment for stone disintegration are compressive fracture, spallation, acoustic cavitation, and dynamic fatigue, of which cavitation is the most important. Diuretics can increase urine flow around the stone and form a fluid film interface between the stone and renal or ureteric wall which improves the possibility for cavitation and enhances stone fragmentation. The use of diuretics followed by ESWL allows the outer shell of the stone to be cracked then the center of the stone becomes more exposed to the subsequent shockwaves allowing entry of urine through the broken surface. Therefore, the diuretic increases the surface area of the stone on which the shock wave can act.[10,11]

The success of the ESWL treatment depends on several factors such as stone size, stone number, and stone composition[12]. From previous studies, diuretics were also used to enhance the efficacy and outcome of ESWL treatment. Dong et al.[13] conducted a meta-analysis which indicated that the use of diuretics during ESWL treatment significantly increased the stone clearance rate (odds ratio, 1.73; 95% confidence interval (CI), 1.35-2.22, $p < 0.0001$) and the stone fragmentation rate (odds ratio, 2.83; 95% CI; 1.30-6.16, $p = 0.009$).

Table 3. Auxiliary treatment post ESWL

Characteristics	Diuretic group n (%)	Control group n (%)	P-value
Double J stent placement	9 (9.3)	11 (11.3)	0.64
Ureterorenoscopy	3 (3.1)	3 (3.1)	1.00
Open stone surgery	1 (1.1)	3 (3.1)	0.31

Furthermore, Azm et al.[14] showed that the use of diuretics with ESWL improved stone clearance rate with the diuretic and ESWL clearance rate being 92.3% compared to 87% ESWL alone without diuretics in 106 ureteric calculi patients. A study by Sohu et al.[15] in 714 patients reported a higher stone free rate in the diuretic group compared to the standard ESWL, 77% compared to 65% respectively ($p < 0.001$).

Zomorrodi et al.[16] investigated 86 patients, divided into 2 equal comparative groups and reported stone fragmentation rates of 81% and 93% and stone clearance rates of 68.2% and 88.4% in the diuretic group and the control group respectively.

In our study ,there was no statistical significant different in overall stone free rate between the diuretic group and control group ($p = 0.886$), but the results did show that CIRF in the diuretic group was significantly higher than in the control group ($p = 0.004$). As mentioned above the reason that CIRF in the diuretic group was significant higher than the control group was because the diuretic increases urine flow around the stone during ESWL which together with cavitation bubbles from the shockwave increases the pieces of fragmented stone shell resulting in more residual stone fragments in the diuretic group. The treatment success rate (stone free rate and CIRF) was significantly higher in the diuretic group than in the control group (81.4%: 64.9%, $p = 0.001$). These results substantiated our hypothesis. It is reasonable to assume that if the period of follow up were longer, some CIRF may be passed and incidence of the stone free rate may increase over time.

Our survey of other literature found that the definition of stone free varied from study to study. Some authors defined stone free as complete clearance of stone but some authors defined stone free as complete clearance of stone

and CIRF. Ahmed et al.[17] defined stone free as no visible stone or residual fragment < 4 mm on x-ray film KUB or ultrasound, and Elkholy et al.[18] defined stone free status as the complete clearance of stone, the treatment success being defined as the stone free state or CIRF < 4 mm These results were in accordance with the findings of our study.

There were several factors found which could interfere with the success of ESWL treatment, for example, stone size, stone number, stone composition, patient related factors such as intrarenal anatomy[19], or stone location especially in the case of lower caliceal stones. Therefore, the choice of treatment which is the minimally invasive, while treating the condition effectively in each patient is an important issue that urologists should consider.

In the future, many factors that enhance the efficacy of ESWL treatment will be developed. The findings of many studies currently being carried out will improve ESWL outcomes and promote a higher success rate of treatment for the maximum benefit for urolithiasis patients[20]. This will ultimately mean that in more and more cases invasive surgery can be avoided. The benefits of this are legion, improving patient experience and the need for hospitalization, reducing costs to the hospital and particularly in this Corona Virus Disease 19 (COVID -19) era where surgery could increase infection rate, a minimally invasive procedure is invaluable.

Conclusions

Diuretics did not improve the stone free rate after ESWL in this study but diuretics improved treatment success rate of ESWL treatment in comparison with standard ESWL.

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Conflicts of Interest

The author declares no conflict of interest.

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