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Effect of Diuretics Therapy on Upper Urinary Tract Stones Before Extra Corporeal Shock Wave Lithotripsy and Compare its Efficacy with Tamsulosin Therapy After Extra Corporeal Shock Wave Lithotripsy (ESWL)

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ABSTRACT

Upper urinary tract stones are one of the most common urological health problems worldwide, having a prevalence of approximately 12% in men and 7% in women¹. Moreover, its prevalence varies with country to country and race to race. It ranges from 5-9% in Europe, 7-13% in North America and 1-5% in Asia. Compare the efficacy of diuretic before ESWL with efficacy of tamsulosin after ESWL in management of upper urinary tract stone. One hundred of patients with stone size between 5mm-15 mm randomized into two group. Group A patients received 40mg of furosemide 5 minutes before ESWL and Group B patients received tab tamsulosin (.4mg) for 21 days after ESWL. ESWL included 3000 shock waves per patient in each session with energy from 8kv-15kv, primary outcome compare in term of fragmentation of stone, stone free rate, requirement of second session. Fragmentation of stone was better in Group A patients, at 57.4% vs 41.3%. Further SFR (Stone free rate) was also higher in Group A patients as compare to Group B patients, at 70.4% vs 65.2%. Requirement of second procedure much less in Group A as compare to Group B. Diuretic seem to be better or equally good adjuncts to ESWL tamsulosin after ESWL.

INTRODUCTION

Upper urinary tract stones are one of the most common urological health problems worldwide, having a prevalence of approximately 12% in men and 7% in women^[1]. Moreover, its prevalence varies with country to country and race to race. It ranges from 5-9% in Europe, 7-13% in North America and 1-5% in Asia^[2]. Patients with kidney stones often suffer from short-term symptoms including acute renal colic, nausea, vomiting and hematuria, as well as long-term complications such as chronic urinary tract obstruction, hydronephrosis and renal damage. Treatment of upper urinary stones consists of various options including ureteroscopic extraction, ureteroscopic lithotripsy and ESWL, open surgery and laparoscopic surgery. Compared with endoscopic and open surgical procedures, SWL is a minimally invasive procedure with reduced requirements for anesthesia^[3]. For reducing the necessity of more invasive treatments such as ureteroscopy, less invasive interventions including inversion therapy, mechanical percussion and drug therapy have been explored. Among these, pharmacotherapy is considered as a promising approach, with medicines such as calcium channel blockers^[4], α -adrenergic blockers, nonsteroidal anti-inflammatory drugs and progesterone being proven to have beneficial effects on the expulsion of stones and efficacy of SWL. Success of ESWL depends on several factors that include stone size, location, hardness of stones which is indicated by HU in NCCT KUB, degree of obstruction, anatomical abnormalities of upper urinary tract, renal function etc. ESWL works on the principle of cavitation, which requires watery environment around the stone. Diuretics increase urinary flow around the stone during ESWL, which improves the likelihood of the cavitation phenomenon occurring. Diuretics are safe and if used as an adjunct to ESWL, can provide a better outcome. Tamsulosin is an α -1-adrenergic antagonist and causes inhibition of smooth muscle contraction in ureter, facilitating passage of stones into bladder, thus being one of the most common drugs used to increase stone clearance after ESWL. Therefore, in the present study, we plan to evaluate our experience with use of diuretics pre-procedure and its effects on stone clearance in the patients presenting with radiopaque upper urinary tract stones ranging from size 5-10mm who underwent ESWL.

MATERIALS AND METHODS

Study Area: The study was conducted at Department of Urology, RG Kar Medical College and Hospital and Kolkata-04.

Study Population: Patients with urinary stone underwent ESWL (with inclusion and exclusion criteria under consideration) in the Department of Urology during the study period.

Study Period: February 2020 to November 2021.

Sample Size:

$$N = (Z_{1-\alpha/2})^2 \times P \times Q / L^2$$

N=Sample size, $Z_{1-\alpha/2}$ (1.96)=Standard Normal deviation considering 95% Confidence level, P=Expected Proportion of stone fragmentation rate as found in study. It is taken as 96.2%, $Q=[100-P]=3.8$, L=Precision in absolute term (3.5).

Using above formula sample size is 114.63. We had taken 100 study subjects.

Inclusion Criteria:

- All patients with upper urinary tract stone having size between 5mm-15mm.
- All radiopaque stones.
- All patients having no growth in urine c/s.
- Normal coagulation profile.
- Willing to give informed consent.

Exclusion Criteria:

- Age <18 years and age >60 years.
- All radiolucent stones.
- Patient who had abnormal coagulation profile.
- Patient with positive urine c/s.
- All patients who have already taking diuretic for other co-morbidity.
- All pregnant female with upper urinary tract stone.
- All patients with electrolytes abnormalities.

Study Design: A Prospective study.

Study Tools:

- A detailed patient history, clinical profile assessment and informed consent.
- A detailed physical examination.
- Urine-culture.
- Coagulation profile work-up.
- X-Ray KUB. [Pre and post procedure]
- NCCT whole abdomen. [Pre procedure].

Study Technique: Before conducting the study, my research proposal was presented to the institutional ethical committee. After ethical committee clearance, the study was aimed at fulfilling the aims and objectives of this research. Subjects fulfilling the inclusion and exclusion criteria were taken as study participants. Informed consent was taken from the subject before including them in the study. After proper history taking, blood picture including coagulation profile, urine culture and X Ray KUB, NCCT KUB, [Pre procedure], patients planned for ESWL in such way that two patients scheduled for ESWL on particular date. Before ESWL both patients received injection gentamicin 40mg, injection diclofenac 75mg IM stat and one of them also received injection furosemide 40mg as short IV and this group of patients classified as

Group A patients and ESWL given to both patients up to level 3 or 3000 shock [subjected to patient tolerance to ESWL shock]. Post ESWL both patients given advice to take oral levofloxacin 500mg for 7 days and patient which does not received furosemide also advice to take oral tamsulosine (.4 mg) daily for 21 days and this group of patients classified as Group B patients, both Group of patients follow up in urology OPD after 21 days, with the help of X- ray KUB ESWL results compared in term of fragmentation of stone, stone clearance and need of another session of ESWL.

Statistical Analysis: For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0., SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarize as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is use as short for Pearson's chi-squared test. Unpaired proportions were compare by Chi-square test or Fischer's exact test, as appropriate. Explicit expressions that can be used to carry out various t-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also the appropriate degrees of freedom are given in each case. Each of these statistics can be use to carry out either a one-tailed test or a two-tailed test. Once a t value is determined, a p-value can be found using a table of values from Student's t-distribution .If the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis. P-value ≤ 0.05 was consider for statistically significant.

RESULTS AND DISCUSSIONS

Table 1: Association Between Age in Group: Group

Age in Group	Group		Total
	Group-A	Group-B	
21-30	26	23	49
31-40	11	8	19
41-50	6	4	10
51-60	11	11	22
Total	54	46	100

Table 2: Association Between Laterality: Group

Laterality	Group		Total
	Group-A	Group-B	
Left	28	33	61
Right	26	13	39
Total	54	46	100

Table 3: Association Between Stone Fully Fragmented at End of 1st Procedure: Group

Stone fully fragmented at end of 1st procedure	Group-A	Group-B	Total
No	23	27	50
Yes	31	19	50
Total	54	46	100

Table 4: Association Between PT Require 2 Procedure: Group

PT Require 2 Procedure	Group-A	Group-B	Total
No	38	30	68
Yes	16	16	32
Total	54	46	100

Table 5: Association Between PT3 Week After 2 Procedure: Group

PT3 Week After 2 Procedure	Group-A	Group-B	Total
Stone Free	14	10	24
Not Stone Free	2	6	76
2 procedure not applicable	38	30	68
Total	16	16	100

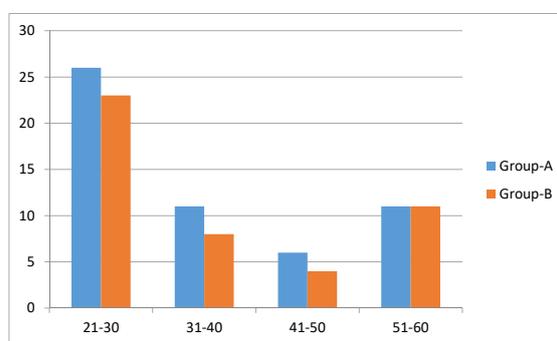


Fig. 1: Age in Group

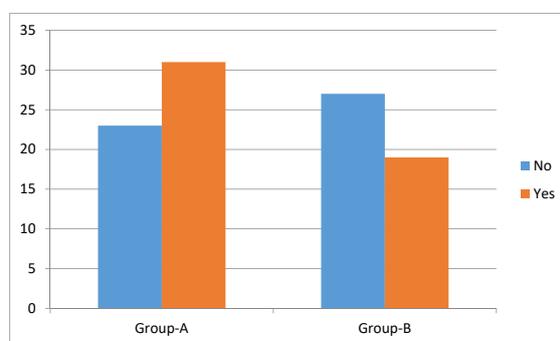


Fig. 2: Stone Fully Fragmented at End of 1st Procedure

In Group-A, 26(48.1%) patients were 21-30 years of age, 11(20.4%) patients were 31-40 years of age, 6(11.1%) patients were 41-50 years of age and 11(20.4%) patients were 51-60 years of age. In Group-B, 23(50.0%) patients were 21-30 years of age, 8(17.4%) patients were 31-40 years of age, 4(8.7%) patients were 41-50 years of age and 11(23.9%) patients were 51-60 years of age. In Group-A, 23 (42.6%) patients were female and 31 (57.4%) patients were male. In Group-B, 18 (39.1%) patients were female and 28 (60.9%) patients were male. In Group-A, 28(51.9%) patients had Left side stone and 26(48.1%) patients had Right side stone. In Group-B, 33(71.7%) patients had Left side stone and 13(28.3%) patients

had Right side stone. In Group-A, 11(20.4%) patients had Stone in LC, 11(20.4%) patients had Stone in MC, 17 (31.5%)patients had Stone in P.U.J. and 15(27.8%) patients had Stone in RP. In Group-B, 13(28.3%) patients had Stone in LC, 14(30.4%) patients had Stone in MC and 19(41.3%) patients had Stone in RP. In Group-A, 31(57.4%) patients had stone fragmented at the end of 1st procedure. In Group-B, 19(41.3%) patients had stone fragmented at the end of 1st procedure. Association of stone fragmentation at the end of 1st procedure with Group was statistically significant ($p=0.0284$) but fragmentation of stone was more in Group A as compared to Group B. In Group-A, 38(70.4%) patients had stone free after 3 weeks of 1st procedure. In Group-B, 30(65.2%) patients had stone free after 3 weeks of 1st procedure. Association of stone free rate after 3 weeks of 1st procedure with Group was not statistically significant ($p=0.5819$). Stone clearance was also better in group A as compared to group B. In Group-A, 16 (29.6%) patients required 2 procedures. In Group-B, 16(34.8%) patients required 2 procedures. In Group-A, 14patients were Stone Free after 3weeks of second procedure and 2patients were not Stone Free after 3weeks of 2nd procedure. In Group-B, 10patients were Stone Free after 3weeks of 2nd procedure and 6patients were not Stone Free after 3 weeks of 2nd procedure. Association of PT 3 weeks after 2nd procedure with Group was not statistically significant ($p=0.1568$).

This prospective study was conducted at Department of Urology, R.G. Kar Medical College and Hospital, Kolkata from February 2020 to November 2021. All patients with upper urinary tract stones having size between 5mm-15mm, all radiopaque stones, all patients having no growth in urine c/s, normal coagulation profile and willing to give informed consent were included in this study. Renal stones are one of the common problems in India because of its geographical location. India lies in a 'stone belt' region, which extends from Egypt, Iran, Pakistan and Thailand to Indonesia and the Philippines. The use of ESWL for treating patients with renal stones has brought about a revolution in the field of urology. About 12% of the population will have urinary stone disease during their lifetime and the recurrence rate reaches 50%. Sohu^[5] showed that of the 714 patients, 67(18.79%) and 66(18.4%) were aged ≤ 25 years in Group-A and Group-B, respectively., whilst 97(27.1%) and 84(23.5%) were respectively aged > 40 years. The patients' mean (SD) age was 34.4 (8.23) years. In our study, in Group-A, the mean Age of patients was 37.4815 \pm 13.0033 years. In Group-B, the mean Age of patients was 37.7391 \pm 13.7217 years. In Group-A, 26(48.1%) patients were 21-30 years of age, 11(20.4%) patients were 31-40 years of age, 6(11.1%) patients were 41-50 years of age and 11(20.4%) patients were 51-60 years of age. In Group-B, 23(50.0%) patients were 21-30 years of age, 8(17.4%) patients were 31-40 years of

age, 4(8.7%) patients were 41-50 years of age and 11(23.9%) patients were 51-60 years of age. We found that out of 100 patients, majority of patients [49(49.0%)] were within age 21-30 years but this was not statistically significant ($p=0.9361$). Sohu^[5] showed that there were 231(64.71%) males in Group-A [patients received 40mg furosemide 30 min before each ESWL session and 1000mL 0.9% NaCl intravenous hydration during the procedure] and 210 (58.82%) in Group-B [the patients only received 0.9% NaCl]. We observed that male population [59(59.0%)] was higher than the female population [41(41.0%)] which was also not statistically significant. Studies from other parts of the world have also shown a higher prevalence amongst males 5-6. Sohu^[5] showed that regarding stone location, 239(61.34%) and 164 (45.94%) were located on the left side and 138(38.68%) and 193 (54.05%) were located on the right side in Group-A and Group-B, respectively. Present study showed that Left Laterality was significantly increased in Group-B [33 (71.7%)] patients compared to Group-A patients [28 (51.9%)] and Right Laterality was significantly increased in Group-A patients [26 (48.1%)] compared to Group-B patients [13 (28.3%)]. ($p=0.0421$). Patients in three of the studies 6-8 received 40 mg furosemide at the initiation of SWL, while one study 128 describes the administration of 20 mg furosemide at the initiation of SWL. Sabharwal^[6]. used shocks at a frequency of 80/min starting at 7 kV with dose escalation up to 16 kV until either the stone fragmented or the maximum of 1,500 or 2,000 shocks was reached (per session) for renal or upper ureteric calculi, respectively. Up to three sessions were performed. Zomorodi^[7] described the administration of 3,500 shocks with an energy of 9-13 kV per session in up to three sessions. Azm^[8] administered shocks at a rate of 90/min at 10 kV with dose escalation up to 18kV (in up to four sessions). Lastly, Yoon^[9] reported the use of 3,000 shocks in one session. The evaluation of the stone clearance for three studies 6-8 was for 3 months and one128 was for three weeks. Although all the RCTs reported the rate of stone clearance and fragmentation, only two RCTs 7-8 described the total number of shocks and sessions required. Our study showed that stones fragmented at end of 1st procedure was more found in patients from Group-A [31(57.4%)] compared to patients from Group-B [19(41.3%)] and this was statistically significant ($p=0.0284$). In the Yoon^[9] Study, the patients underwent fewer SWL sessions and significant differences in stone clearance between patients who received diuretics or placebo were reported. Residual stones were evaluated three months post-treatment in all the studies included in our final analysis. In our study also showing that higher number of Group-B patients [16(34.8%)] required 2 procedures compared Group-A patients [16(29.6%)] but this was not statistically significant ($p=0.5819$). The influence of

diuretic therapy on the success rate of ESWL was also investigated by Zomorodi^[8]. The standard ESWL protocol was used in a group of 43 patients and another group of 43 patients received 40 mg furosemide before ESWL. The SFR was 68.2% and stone fragmentation rate was 81% in the control group, but in the treatment group, the rates were 88.4% and 93.1%, respectively. Regardless of the location of the ureteric stones, they reported that the addition of the diuretic to ESWL therapy improved both stone fragmentation and SFRs. In another clinical trial, including 115 patients conducted by Jafri^[10], the effect of furosemide on the success rate of ESWL in patients with renal or ureteric stones was studied. The treatment group receiving diuretic had a SFR of 71.9% compared with 39.7% amongst the controls (P=0.007). Whereas the success rate for those with renal stones was 63.3% in the treatment group and 43.8% in the controls, those with ureteric stones had a success rate of 81.5% vs 20%. The increase in success found in the furosemide treated patients was seen particularly when their BMI was >30kg/m² (81.3% vs 38.9%). We also found that stone free rate after 3 weeks of 1st procedure was more observed in patients from Group-A [38(70.4%)] compared to patients from Group-B [30(65.2%)] but this also had no statistically significant difference(p=0.5819). We observed that in Group-A, 14 patients were stone free after 3 weeks of 2nd procedure and in Group-B, 10 patients were stone free after 3 weeks of 2nd procedure.

CONCLUSION

In our study, the administration of 40mg Furosemide (Group A patients) improved fragmentation and clearance of stones after ESWL as compared to the patients who did not received diuretic before procedure(Group B patients). So diuretics seem to be better or equally safe adjuncts to ESWL treatment of upper urinary tract stone disease as pre-procedure medical therapy compared with 21 days of Tamsulosin therapy.

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