

EFFECTIVENESS OF LOSARTAN IN EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL) INDUCED NEPHRON INJURY

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ABSTRACT

Objective: To compare losartan and multi-vitamins as antioxidants in decreasing albuminuria in extra corporeal shock wave lithotripsy (ESWL) related renal injury.

Material and Methods: This is a randomized control trial done in the Department of Urology "Team C" at Institute of Kidney Diseases (IKD), Hayatabad Medical Complex Peshawar from June 2018 to March 2020. All the patients with 10 to 15 mm renal stones were included. The patients were divided into two groups; Group A of 90 patients (control) were given multivitamins (Zinc, Selenium, Vitamin A & C) two hours before and one tablet every eight hours after ESWL up to one week. Group B of 90 patients were given Tab. losartan 50 mg two hours before ESWL and once daily after ESWL for one week. The on-spot albuminuria was evaluated before ESWL, at 2-4 hours and one week after standard ESWL (3000 shocks). A structured pro forma was used for the data and the analysis of data was done on SPSS.

Results: Almost all the demographics like age, gender, laterality, BMI in both the groups were similar, the albuminuria before ESWL in Group A was 13.9 mg/dl and Group B was 14.1 mg/dl. The albuminuria in Group A was 547 mg/dl after 2-4 hours of ESWL and 581.2mg/dl in Group B (P 0.098). In Group A after one week of ESWL the albuminuria was 88.7 mg/dl versus the albuminuria 41.9 mg/dl in Group B ($p < 0.001$).

Conclusion: Losartan (ARB) is superior to the anti oxidants as a kidney protective agent against ESWL related renal injury by remarkably reduced albuminuria.

Keywords: Urolithiasis, Lithotripsy, Losartan, ESWL, Complications, Kidney Stone.

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INTRODUCTION

Urolithiasis is a disease of antiquity and the earliest reference can be found in Hippocratic Oath that "I will not cut upon the bladder stone".¹ The prevalence of urolithiasis in South East Asia is 16% and almost accounts for 50 percent of all the Urological OPDs and Urological Surgeries in Pakistan.^{2,3} Extracorporeal Shock Wave Lithotripsy was introduced in 1980s and remained first line of management for treatment of renal and upper ureteric stones for 2 decades. The introduction of percutaneous surgery and miniaturizing of endoscopic equipment have changed the paradigm from ESWL to the era of Mini and Micro PCNLs. Despite the fact, ESWL is still considered as a crucial treatment option in management of urolithiasis. ESWL is considered first line management in < 15mm sized renal stones irrespective of location. ESWL is con-

sidered minimal invasive and safe modality⁴. The overall minor complication rates of ESWL is 15-38 %. The long term complications are always a subject of debate in literature. Some studies have reported increase rate of hypertension as 4% after 10 years of ESWL.⁵ However, there is no clear evidence whether there is any direct relationship between hypertension and ESWL.

The newer development in the lithotripters like latest versions of electromagnetic lithotripters have reportedly raised the efficacy and reduced the complication rates. Yet ESWL is associated with injury to nephron. Different markers can be used to know about renal injury due to ESWL for example measurement of urinary albumin, neutrophil gelatinase-associated lipocalin (uNGAL) and MRI (dynamic contrast enhanced). The reno-protective effectiveness in EWSL and several medications including Losartan which is angiotensin receptor blocker and multi vitamins comprising of Selenium, Vitamin A & C are reported to be helpful in decreasing the ESWL related renal injury^{6,7}. However, the beneficial effect of selenium based multivitamins is only shown in animal models in most of the studies.

The Institute of Kidney Diseases Peshawar is the largest tertiary hospital with enormous work load man-

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aging the patients of renal stones. The overzealous use of ESWL mainly in private sector of Khyber Pakhtunkhwa has discredited ESWL. The rationale of our study is based on a research question that which of either, the Selenium based multi-vitamins or Losartan is better in decreasing renal injury associated with ESWL. As uNGAL and MRI (dynamic contrast) are not available in our setup, so we have selected the estimation of urinary albumin in urine as a marker, easily available in all laboratories in Peshawar. The present study when published will be shared with the owners and operators of lithotripters about use and also the prevention of nephron injury.

MATERIAL AND METHODS

This is a randomized control trial done in the Department of Urology "Team C" at Institute of Kidney Diseases (IKD), Hayatabad Medical Complex Peshawar from June 2018 to March 2020. A total of 180 patients were equally divided into two groups by lottery method. We included all the patients with stone size ranging from 10 to 15 mm in renal pelvis and upper, middle and lower calyces with favorable anatomy. We excluded patients with stone density more than 1000 HU as those stones are hard to be fragmented by ESWL. All patients with pre-procedure albuminuria, marked hydronephrosis, diabetes, congenital anomalies and hypertension were excluded. We also excluded obese patients as a contraindication to ESWL. All the patients who full filled the mentioned criteria and had given consent were included in the study. A total of 180 patients were equally divided into two groups by lot-

tery method. Group A of 90 patients (Control) were given multi-vitamins (Zinc, Selenium, Vitamin A & C) in dose of Selenium 0.02 mg, Vitamin C 5 mcg, Vitamin A 1mg and Zinc 3 mg two hours before and one tablet every eight hours after ESWL for one week. Group B of 90 patients, were given Tab Losartan 50 mg two hours before ESWL and once daily after ESWL for one week. All the patients were subjected to electromagnetic ESWL by single operator. 3000 shocks were given to all the patients in first session. The number of shocks was tailored according to degree of fragmentation in subsequent second and third sessions. The on-spot albuminuria was evaluated before ESWL, at 2-4 hours at and one week after 1st session of standard ESWL of 3000 shocks. Our outcome variables were categorical like laterality, gender, location of stone and numerical values were age, stone size, BMI. For comparing means T test was used. Chi square test was used for gender laterality and location of renal stones. A structured pro forma was used for the data and the analysis of data in SPSS.

RESULTS

The categorical demographic variables such as gender, laterality of stone and location of stone is shown in Table 1. The continuous variables like age, stone size and session with mean and standard deviation is shown in Table 2. The albuminuria was assessed before ESWL and at 2 hours and 1 week after 1st session of standard ESWL. The result of mean and SD of pre and post-EWSL in are shown in Table 3.

Table 1: Categorical Demographic Variables.

Categorical Variable n(%)	Group A (n=90) Control (Selenium based Multivitamins)				Group B (n=90) Case (Losartan)				P value Chi Square
Laterality									0.414
Right	47 (52.2%)				44 (48.8%)				
Left	43 (47.7%)				46 (52.1%)				
Gender									0.73
Male	55 (61.1%)				57 (63.3%)				
Female	35 (38.8%)				33 (36.6%)				
Stone location	Renal Pelvis	Upper Calyx	Middle Calyx	Lower Calyx	Renal Pelvis	Upper Calyx	Middle Calyx	Lower Calyx	Anova >0.05
	41 (45.5%)	18 (20%)	20 (22.2%)	11 (12.2%)	37 (41.1%)	21 (23.3%)	22 (24.4%)	10 (11.1%)	

Table 2: Numerical Values of Age, Stone Size and BMI.

Numerical value Mean (SD)	Group A (n=90) Control (Selenium based Multivitamins)	Group B (n=90) Case (Losartan)	P value
Age	37.4±9.8	39.8±5.1	0.75
Stone size	13.5±2.1	11.2±3.2	0.71
Body mass index	27.9 (6.1)	26.8 (6.3)	0.71

Table 3: Cross tabulation of Pre and Post ESWL Albuminuria in both groups.

Numerical value Mean (SD)	Group A (n=90) Control (Selenium based Multivitamins)	Group B (n=90) Case (Losartan)	P value
Pre ESWL Albuminuria	13.6 (6.1)	14.8 (6.7)	0.80
2 hours Post ESWL	547.6 (46.1)	581.2 (48.7)	0.001
7 days Post ESWL	88.7 (44.3)	41.9 (36.2)	0.001

DISCUSSION

Urolithiasis and its complications are the most common illnesses presenting to urological units in Pakistan. Although, the technical advancement in endo-urological equipment's has limited the indications of ESWL, yet all those endo-urological procedures require admission, operation theatres and anesthesia respectively. The huge burden of urolithiasis in our setup overwhelms the waiting periods for surgeries. So keeping in mind the true indications of ESWL and resource limitations for endo-urological procedures, Extra Corporeal Shock Wave Lithotripsy is still considered minimal invasive, safe and reasonably effective treatment modality. The present study has put an emphasis on enhancing the safety profile of ESWL as we being doctors believe in 1st fundamental point of Hippocratic oath "First do no harm".

The epic part of our study is that it's a randomized control clinical trial of larger sample size comparing the kidney-protective effectiveness of selenium based multivitamins versus losartan in reducing the ESWL induced nephron injury.

The limitation of the study is that we didn't carry out this study with double blinding and placebo control. Moreover, the diversity in laboratory findings for detecting albuminuria and non-availability of better parameters for assessing nephron injury also renders a limitation to our study. Still we have tried to control this confounder with selection of the best available laboratory with no conflict of interest.

The clinical evidence of ESWL on renal tissue is manifested by hematuria. The gross hematuria which persists for a couple of days, however the microscopic hematuria persists for few weeks. The Post ESWL sub capsular hematomas range upto 25% on serial MRIs and CT scan⁵. This intra-renal/sub capsular hematomas lead to tissue ischemia that can result in apoptosis. Studies have found that the major hematomas due to injudicious use of lithotripters result in scar formation on the renal cortex. However, if ESWL is used as per guidelines the nephron injury due to ESWL remain a focal process that leaves most of the renal tissue intact⁸.

The ESWL induced nephron injury can be minimized by a number of ways. It can be achieved by improved focal length in newer generations especially the shift from spark gap technology to electromagnetic and piezoceramic lithotripters. Newer procedural techniques

like Shock wave Lithotripsy with reno-protective pause is also gaining interest among urologists⁹.

The new insights of reno-protective mechanism of selenium based multivitamins through free-radical scavenging activity, nifedipine, verapamil and mannitol has raised the interest of researchers. Lately, losartan (ARB) has appeared to be effective in ESWL related nephron injury. The physiology of this protective nature is due to prevention of ischemia or reperfusion injury. Effectiveness of both treatments was analyzed by its ability to hamper a significant increase in albuminuria, which shows leakage of albumin from the injured renal glomeruli.

Our study has shown that Losartan is superior ($p < 0.001$) to Selenium based multivitamins at 1 week interval in reducing the albuminuria after ESWL. This finding is in accordance with international literature^{4, 10-12}. Losartan, Verapamil, Nifedipine and Mannitol were found equally effective in recent literature in human model too¹²⁻¹⁵. Although Kehinde EO has reported superiority of Selenium based multivitamins in ESWL induced injury, but the sample size in that article was very low i.e. 39 patients with stone size of 30 mm and they didn't compare the multivitamins with either of Losartan or Verapamil¹⁶⁻¹⁸.

Our study will benefit all the Urologists, Nephrologists, Specialists in Lithotripsy and Health care providers that are involved in ESWL and post ESWL care of patients with urolithiasis^{19,20}. Large sample size RCT studies are needed to assess long term benefits of this kidney-protective medication after ESWL.

CONCLUSION

ESWL is minimal invasive and a safe mode in management of urolithiasis. Selenium based multivitamins and Losartan both possessed reno-protective mechanism in reducing albuminuria after ESWL. However, Losartan showed superiority at 1 week Post-ESWL over multivitamins.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Ali L: Concept, Methodology, data Collection.

Hayat F: Manuscript writing, data Collection.

Khan S: Data Collection.

Hayat S: Analysis of data.

Wahab MU: Data Collection, manuscript writing.

Hassan A: Collection of data.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.