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CLINICAL STUDY

Evaluation of the Process of Recycling and Renal Parenchymal Injury after ESWL with Metabolites Excreted in the Urine

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Abstract

Objectives: To show renal parenchymal injury depending on extracorporeal shock wave lithotripsy (ESWL). *Methods*: The patients with one renal stone and in whom ESWL is planned among the patients in whom renal stone was determined. Their 24-h urine samples were collected just before and after the ESWL treatment. Cit (citrate), UrA (uric acid), RBP (retinol-binding protein), NAG (*N*-acetyl-β-Ð-glucosaminidase), Cr (creatinine), Na (sodium), K (potassium), P (phosphor), Ca (calcium), and Cl (chlorine) metabolites excreted in urine were evaluated after urine samples were taken on the study day. Changes in the metabolites excreted; the number, frequency, and duration of ESWL shock wave; the energy; and the body mass index were recorded. The results for $p < 0.05$ will be accepted as statistically significant. *Results*: Two sessions of ESWL were applied to a total of 20 patients. When metabolites excreted in the urine before (B1E) and after (A1E) the first session of ESWL, and before (B2E) and after (A2E) the second session of ESWL, were evaluated, no statistically significant result for Ca and Cl excretion was noted. For NAG and Cr, a significant difference was observed in terms of metabolite excretion between B1E and B2E. For other metabolites, we saw that there is no difference between B1E and B2E. While a significant metabolite change was observed for RBP, NAG, Cr, and Na as long as A1E and A2E ESWL session number increases, other metabolites were not significant. *Conclusion*: Shock waves induce significant damage to the renal and adjacent tissues as indicated by a significant increase in cell-escaped enzymes and electrolytes and the extent of damage depends on the energy and the number of shock wave exposure.

Keywords: extracorporeal shock waves lithotripsy, serum enzymes, serum electrolytes, renal function, urinary electrolytes

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL), introduced into clinical practice in the early 1980s, is a noninvasive and effective method in the management of patients with urolithiasis. Studies with large patient population showed that up to 90% of patients were successfully treated by ESWL. ESWL is generally well tolerated, although reduced renal function, hemorrhage or perirenal hematomas, urinary obstruction, hypertension, and urosepsis can occur. Further studies demonstrated ultramicroscopic changes in renal tubules and glomerules.[1] Urinary enzymes levels have been assessed throughout the spectrum of kidney injuries due to antibiotics, heavy metals, analgesics, chemotherapy, and graft rejection, but as soon as kidney function improves, the excretory enzymes return to their normal level.[2] Hydrolytic lysosomal enzymes levels, like *N*-acetyl-glucose aminidase and galactosidase are precise indicators of these enzymes and have the greatest concentration in proximal tubules of mammals. Another enzyme used in evaluating kidney parenchymal damage is alanine amino peptidase (AAP).[2,3]

There are three primary types of shock wave generation: electro hydraulic (spark gaps), which works ultrasonically; AC arm, which works manually; and dual electrodes. In this study, the first pilot study results show renal parenchymal injury and recycling with substances (metabolites, enzymes, and electrolyte) the 24-h urine in the patients in which stonelessness was achieved after two sessions of ESWL.

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MATERIALS AND METHODS

Twenty patients, in whom no ESWL was performed before, who have ureteropelvic junction (UPJ) stone in one kidney, and whose stone load is under 2 cm, were included in the study. Those with single kidney, those with multicalyceal stone, those with non-opaque stone, those with anomaly kidney, those who are absolutely and relatively contraindicated for ESWL, those with liminal renal failure in routine biochemical evaluation, those whose creatinine is over 2.0 mg/dL, those with hematologic problem, patients with urinary infection and patients who are unable to tolerate ESWL under local anesthesia were excluded from the study. The second ESWL session was applied after 15 days to all the patients. Before each ESWL session, the patients were given paracetamol, deksketoprofen trometamol, and tramadol hidroclorur according to the pain scale. In non-contrast enhanced computed tomography, which was done 15 days after the second ESWL session, it was considered to be stone-free as there was no stone or if there was any it was tinier than 2 mm. Electrohydraulic lithotriptor device was used for ESWL.

Twenty-four hour urines of the patients were collected before (B1E) and after (A1E) the first session ESWL and before (B2E) and after (A2E) the second session ESWL. They were stored at –80°C. The urine samples were evaluated at room temperature before working on them. For the patients, Cit (citrate), UrA (uric acid), RBP (retinol-binding protein), NAG (*N*-acetyl-β-Đ-glucosaminidase), Cr (creatinine), Na (sodium), K (potassium), P (phosphor), Ca (calcium), and Cl (chloride) excreted in the urine were evaluated. For patients in whom ESWL was administered, the variables of energy (kV); shock waves number, duration, and frequency; age; and body mass index were recorded.

Biochemical Method

Citrate (Cit) in the 24-h urine samples was determined with enzymatic UV spectrophotometric kit of FAR firm (FAR S.r.l., Verona, Italy). Retinol-binding protein was determined with an enzyme-linked immunosorbent assay (ELISA) kit of ASSAY PRO firm (Assay Max Retinol-Binding Protein 4 ELISA Kit Catalog No: ER3005-1). *N*-acetyl glucosaminidase was determined with an ELISA kit (E90069Hu 96 Tests) of Uscn Life Science Inc (Houston, TX, USA). Na, K, and Cl were determined with the ion-selective electrode method in Hitachi Roche Modular ISE 900 autoanalyzer. Uric acid (ur. acid), Ca, and P were determined with the photometric method in Hitachi Roche Modular ISE 900 autoanalyzer (Dallas, TX, USA).

Statistical Analysis

Analyses of data were done with SPSS 11.5 Inc. (SPSS, Chicago, IL, USA) for Windows ver.15 package program. Definitive statistics were expressed as the mean ± standard deviation for the variables with normal distribution and as the median (min–max) for the variables with non-normal distribution. These were evaluated with variance analysis in repeated measures for the variables with normal distribution for comparison of four times, while Friedman's test was used for the variables with non-normal distribution. Post hoc test was done for the variables where a difference is present between times; Bonferroni test was applied for variance analysis in repeated measures, Friedman post hoc test was also done.[4] Results for $p < 0.05$ will be accepted as statistically significant.

RESULTS

Two sessions of ESWL were applied to a total of 20 patients whose mean age is 52.0 (29–68), stone load is 15.0 (10–20) mm, body mass index is 25.6 (20.5–28.8), shock wave number is 1975 (1500–2500), and mean frequency is 77.5 (70–90) kW/h. With two sessions of ESWL, stonelessness was achieved. No statistically significant difference was observed in terms of energy, number, and frequency of shock waves and the duration between sessions used in patients for ESWL ($p > 0.05$) (Table 1).

Substances excreted in the urine before (B1E) and after (A1E) the first session of ESWL and before (B2E) and after (A2E) the second session of ESWL were recorded. The database was specified as table and graph (Table 2 and graph). Changes in all substances excreted in the urine B1E and A1E and B2E and A2E except Ca and Cl were monitored for statistical significance (Table 2 and graph). Pairwise comparison was performed for each metabolite in its own right in B1E and A1E, and B2E and A2E, groups. B1E–A1E was $p < 0.05$, B1E–A2E was $p < 0.001$, A1E–B2E was $p < 0.05$, and B2E–A2E was $p < 0.001$ for citrate excretion in the urine. B1E–A1E was $p < 0.001$, B1E–A2E was $p < 0.001$, A1E–B2E was $p < 0.05$, A1E–A2E was $p < 0.05$, and B2E–A2E was $p < 0.001$ for RBP. B1E–A1E was $p < 0.01$, B1E–B2E

Table 1. The distribution of energy, frequency, shock, and time variables in patients who were performed ESWL.

n		First session	Second session	*p*-Value
Energy (kV)	Median (min–max)	18.50 (16–20)	18 (16–20)	0.617
Frequency	Median (min–max)	77.5 (70–90)	75 (70–90)	0.285
Shock waves	Median (min–max)	1975 (1500–2500)	1900 (1550–2300)	0.118
Time	Median (min–max)	45 (30–55)	45 (35–55)	0.763

Table 2. The distribution of metabolites excreted by urine before and after the second session ESWL and binary comparisons of them.

	b1e	a1e	b2e	a2e	*p*-Value	Binary comparisons
Cit. median (min–max) mg/L	102.5 (38–312)	78.5 (35–399)	97 (45–360)	63.5 (30–453)	<0.001	b1e–a1e $p < 0.05$ b1e–b2e $p > 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p < 0.05$ a1e–a2e $p > 0.05$ b2e–a2e $p < 0.001$
RBP median (min–max) ug/mL	73.5 (37–108)	91 (43–133)	77 (39–166)	106.5 (54–188)	<0.001	b1e–a1e $p < 0.001$ b1e–b2e $p > 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p < 0.05$ a1e–a2e $p < 0.05$ b2e–a2e $p < 0.001$
NAG mean ± SD ng/mL	17.17 ± 10.12	23.88 ± 11.45	21.63 ± 9.75	37.17 ± 15.78	<0.001	b1e–a1e $p < 0.01$ b1e–b2e $p < 0.01$ b1e–a2e $p < 0.001$ a1e–b2e $p > 0.05$ a1e–a2e $p < 0.001$ b2e–a2e $p < 0.001$
Cre median (min–max) mg/dL	68.05 (38.15–93.72)	79.68 (46.24–25.36)	78.258 (45.66–138.92)	94.09 (68.31–204.13)	<0.001	b1e–a1e $p < 0.001$ b1e–b2e $p < 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p > 0.05$ a1e–a2e $p < 0.05$ b2e–a2e $p < 0.001$
UrA mean ± SD mg/dL	39.25 ± 13.50	36.10 ± 12.92	40.69 ± 11.25	33.55 ± 11.05	<0.001	b1e–a1e $p > 0.05$ b1e–b2e $p > 0.05$ b1e–a2e $p > 0.05$ a1e–b2e $p < 0.01$ a1e–a2e $p > 0.05$ b2e–a2e $p < 0.001$
Na mean ± SD mmol/L	133.30 ± 23.45	120.70 ± 22.25	130.60 ± 19.85	106.75 ± 19.19	<0.001	b1e–a1e $p < 0.001$ b1e–b2e $p > 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p < 0.001$ a1e–a2e $p < 0.001$ b2e–a2e $p < 0.001$
K median (min–max) mmol/L	39.05 (18.99–73.25)	34.67 (15.53–65.45)	37.92 (19.79–68.67)	27.27 (14.08–57.81)	<0.001	b1e–a1e $p < 0.001$ b1e–b2e $p > 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p < 0.01$ a1e–a2e $p > 0.05$ b2e–a2e $p < 0.001$
P median (min–max) mg/dL	25.14 (10.37–49.28)	31.55 (17.22–58.43)	29.50 (11.90–56.27)	43.72 (19.38–62.20)	<0.001	b1e–a1e $p < 0.001$ b1e–b2e $p > 0.05$ b1e–a2e $p < 0.001$ a1e–b2e $p < 0.05$ a1e–a2e $p > 0.05$ b2e–a2e $p < 0.001$
Ca median (min–max) mmol/L	1.92 (0.84–2.89)	1.96 (0.82–2.61)	1.99 (1.12–2.78)	1.95 (1.12–2.78)	0.461	
Cl mean ± SD mmol/L	140.60 ± 29.13	137.90 ± 21.09	137.95 ± 22.02	143.70 ± 20.88	0.276	

Notes: b1e, before (B1E) the first session ESWL; a1e, after (A1E) the first session ESWL; b2e, before (B2E) the second session ESWL; a2e, after (A2E) the second session ESWL.

was $p < 0.01$, B1E–A2E was $p < 0.001$, A1E–A2E was $p < 0.001$, and B2E–A2E was $p < 0.001$ for NAG. B1E–A1E was $p < 0.001$, B1E–B2E was $p < 0.05$, B1E–A2E was $p < 0.001$, A1E–A2E was $p < 0.05$, and B2E–A2E was $p < 0.001$ for creatinine. A1E–B2E was $p < 0.01$ and B2E–A2E was $p < 0.001$ for Uric acid. B1E–A1E was $p < 0.001$, B1E–A2E was $p < 0.001$, A1E–B2E was $p < 0.001$, A1E–A2E was $p < 0.001$, and B2E–A2E was $p < 0.001$ for Na.

B1E–A1E was $p < 0.001$, B1E–A2E was $p < 0.001$, A1E–B2E was $p < 0.01$, and B2E–A2E was $p < 0.001$ for K. B1E–A1E was $p < 0.001$, B1E–A2E was $p < 0.001$, A1E–B2E was $p < 0.05$, and B2E–A2E was $p < 0.001$ for P. No statistically significant result was determined for Ca and Cl excretion among substances excreted in the urine in patients to whom ESWL was administered.

Double j ureteral stent was inserted into none of the patients before ESWL. Ureterorenoscopy (URS) was performed to one of the patients after ESWL because of the stone street. No stone analysis was performed on the patients.

DISCUSSION

After its clinical application in the last decade, ESWL became the first choice of treatment in patients with urolithiasis. It seems to be a safe procedure although many side effects have been reported in clinical trials and animal models. The most common side effect is gross or microscopic hemorrhage due to the effect of shock waves on the renal parenchyma. Other possible side effects are reduced renal function, urinary obstruction, hypertension, and increased rate of stone formation. Aside from these side effects, ultramicroscopic changes in glomerules and tubules could occur.[5] Biochemical evidence of renal injury is apparent immediately after ESWL. Blood and urine markers such as renin, creatinine, *N*-acetyl-β-Ð-glucosaminidase (NAG), galactosidase (BGAL), β-2-microglobulin (B2M), and proteinuria return to near-normal levels within a few days.[6,7] In our study, we examined samples for Cit (citrate), UrA (uric acid), RBP (retinol-binding protein), NAG (*N*-acetyl-β-Ð-glucosaminidase), Cr (creatinine), Na (sodium), K (potassium), P (phosphor), Ca (calcium), and Cl (chloride) and found a significant change with the change in substances, excluding Ca and Cl, in patients to whom ESWL was administered.

Renal tubular damage is a well-known side effect of ESWL. *N*-acetyl-β-Ð-glucosaminidase (NAG) was localized in the cortical tubular cellular lysosomes and the excretion of NAG was increased when the necrosis of the tubular cells, especially of the proximal tubules that occurred (5). Excretion decreased by day 7, although it was still statistically higher than the pretreatment level. P-2-microglobulin (P2M) level was higher in the patient group before ESWL than in the control group, and a further statistically significant increment was observed 24 h after treatment. The excretion of NAG and P2M returned to baseline levels by the seventh day. The brush border enzyme alkaline phosphatase (AP) also increased 24 h after treatment and the excretion was normalized by day 7. Transient tubular damage as represented by an increased excretion of tubular enzymes was also documented in the previous studies. However, the increment in the excretion of urinary enzymes is not a fact, since some investigators observed no change.[8,9]

Here we note the first finding: a significant difference was observed in terms of substances excretion between B1E and B2E for NAG and Cr. This means that a period of 15 days was not enough for NAG and Cr for the recovery period of the kidney. In other words, substances apart from NAG and Cr can be indicators to give us information about the recovery period of the kidney. An increased risk of cellular injury occurs at energy levels of greater than 2000 shock waves at 20 kilovolt (kV), thus causing an increment in the level of enzymes in the serum. The low-energy treatment resulted in only a mild increase in the enzyme level including less cellular injury. In general, as the shocks increase from 2000 to 3500 shock waves, the lesion size increases. The most profound functional change noted was a 70% decrease in renal function and protein excretion exceeding 1.5 g, 1 h after 2000 shock waves at 24 kV were given.[10] A majority of shock wave lithotripsy (SWL) patients had elevated serum enzymes, implying significant acute trauma to the kidney and adjacent tissues such as liver and skeletal muscles.[11] In our study, no statistically significant difference was observed in terms of number, frequency, and duration of shock wave, and energy between sessions used in patients for both ESWL sessions. We reached at the rate of stonelessness in patients in two sessions without exceeding approximately 2000 shock waves and 19 kV of energy; however, our stone load also was low. Solitary stone and stone dimension were less than 20 mm. When B1E and A1E were compared, and so were B2E and A2E, however, we found a significant change in all substances excreted in the urine, demonstrating renal parenchymal injury, except Ca and Cl.

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves. However, as the shock wave frequency increases, tissue damage increases and stone disintegration improves at lower frequencies.[12] In our study, when we looked at the change in substance excretion between A1E and A2E, while a significant substance change was monitored for RBP, NAG, Cr, and Na, as long as the ESWL session number increased, the excretion of other metabolites was not affected by the ESWL session number. That is, we can also state that RBP, NAG, Cr, and Na urine indicators can be used as indicators of renal parenchymal injury within the ESWL session number. In addition, when we looked at substances excreted in the urine samples for B1E and A2E, we observed a statistically significant difference in substances other than uric acid. In brief, we considered that ESWL may have a cumulative effect in terms of renal parenchymal injury. Nevertheless, as long as its cumulative effect increases, uric acid may not be a good indicator to show parenchymal injury. It is generally agreed that

cell damage, soon after ESWL, correlates well with the changes in cell-escaped enzymes, increase in serum enzyme activities and excretion of proteins, indicating tubular and glomerular damage of kidney.[13] Studies on animals and humans reveal a reduction of glomerular filtration rate (GFR) and renal plasma flow soon after ESWL, especially when pyelonephritis coexists.[14] However, ESWL does not affect GFR over the long term, and immediate renal damage appears to get resolved over a few days to a couple of months.[15] Renal function remains unaffected when ESWL is applied to specific clinical situations. Definitive treatment of urolithiasis after relief of obstruction in patients with renal insufficiency further improves renal function.[16] Studies showed that the impact of a slow mode treatment rate on the efficacy of extracorporeal shock wave lithotripsy and with a minimal increase in procedure time, a greater efficacy can be achieved for the treatment of stones with a slower shock delivery rate.[17] In our study, microscopic hematuria was found almost in all patients while macroscopic hematuria was only seen in a few patients. Macroscopic hematuria recovered within a day. No complication such as gross hematuria lasting for days or perirenal-renal hematoma was observed. Less stone load, the existence of patients only with one stone, failure of ESWL to be performed in high shock wave, frequency, and duration, and no adversity associated with renal failure in blood biochemistry of all patients may have reduced the complication rate. We assessed Cit (citrate), UrA (uric acid), RBP (retinol-binding protein), NAG (*N*-acetyl-β-Đ-glucosaminidase), Cr (creatinine), Na (sodium), K (potassium), P (phosphor), Ca (calcium), and Cl (chloride) substances in our study to show renal parenchymal injury after ESWL. We also compromised on which substances can be a guide in the recovery period of the kidney.

Lee C. et al. found that the efficacy of ESWL is decreased in patients with serum creatinine concentrations of 2.0–2.9 mg/dL, and the complication rate is higher in patients with serum creatinine >4.0 mg/dL. Preoperative counseling may include a discussion of the impact of renal insufficiency on the success and complication rates associated with ESWL.[18] Earlier, the Cevik et al. study demonstrated that ESWL, performed by either a single-shot or a twin-shot shock wave technique, has a transient detrimental effect on renal function. In addition, they observed that although there was no statistically significant difference in the results between the groups, urinary levels of alanine and aspartate aminotransferases, β-2-microalbumin, > γ-glutamyltranspeptidase, Na^+,K^+, and Ca^{++} rose acutely after ESWL, reaching maximum levels on the third day, and returning to the baseline by the seventh day following the treatment in both groups.[19] In our pilot study, we saw that other substances (citrate, uric acid, RBP, Na, K, P) excreted in the urine excluding NAG and Cr, return to normal level by waiting for 15 days between two ESWL.

SUMMARY OF OUR STUDY

The First Finding

A significant difference was observed in terms of substance excretion between B1E and B2E for NAG and Cr. This means that, a period for 15 days was not enough for NAG and Cr in terms of the recovery of kidney. No difference was found in terms of changes in other substances after a period for 15 days. That is to say, excretions of these substances in kidney return to normalcy after 15 days. In addition, substances except NAG and Cr may be indicators to give us information about the recovery period of kidney.

The Second Finding

When we look at the changes in metabolite excretion between A1E and A2E, significant substance change was found for RBP, NAG, Cr, and Na as long as the ESWL session number increased while no significant change was observed for other substances. That is to say; RBP, NAG, Cr, and Na can be used as urine indicators of renal parenchymal injury as long as the ESWL session number increases.

The Third Finding

When we looked at substances excreted in the urine between B1E and A2E, statistically significant difference in metabolites other than uric acid was seen. That is, uric acid may not be an indicator to evaluate renal parenchymal effect after a total of two cumulative ESWL sessions.

Shock waves induce significant damage to the renal and adjacent tissues as indicated by significant increase in cell-escaped enzymes and electrolytes, and the extent of damage depends on the energy and number of shock wave exposures. Although our study is a pilot study, it showed a significant change in other substances we evaluated apart from Ca and Cl, depending on renal injury after ESWL. Uric acid, citrate, Na, K, and P returned to normal level in the period of break taken between the two ESWLs. To show renal parenchymal recovery period, however, NAG and Cr are not good biomarker substances.

CONCLUSION

According to our study, waiting for 15 days to apply the second ESWL was considered to be safe and prospective randomize trials of a large patient series are required.

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