

Evaluation of Acute Kidney Injury (AKI) Markers in Children following Extracorporeal Shock Wave Lithotripsy (ESWL): A Prospective Controlled Study

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ABSTRACT

Objective: To determine the effect of ESWL on kidney damage in children and use potential AKI biomarker levels as diagnostic indicators. **Methods:** We enrolled thirty consecutive child patients who underwent ESWL (Group1) with small renal calculi. As a control, thirty child patients (Group 2) with no known urogenital disease and no known history of urologic pathology also participated in this study. **Result:** The mean age of patients was 7.9±4.3 and 7.5±2.4 years in group 1 and group 2, respectively (p=0.09). The mean stone size was 88.1±65.2 mm² in group 1. Mean levels of KIM 1/Cr were recorded at three times: before ESWL, 2 hours after ESWL, and 24 hours after ESWL. Twenty four hours after surgery, KIM-1/Cr levels increased significantly in urine compared to pre-operative levels (p=0.04). NGAL/Cr mean levels were not elevated significantly after surgery, but there were significant differences between Group 1 patients and Group 2 patients 24 hours after surgery (p<0.01). The NAG/Cr levels were higher in the study group than in the control group and increased significantly after the operation. The mean levels of LFABP /Cr in urinary specimens did not change significantly after ESWL. **Conclusion:** ESWL is safe and curative for urolithiasis in children, but there is no doubt that ESWL can lead to acute kidney injury. Our data suggests that increased NAG/Cr and KIM 1/Cr levels can help in assessing the amount of damage done to the kidney after ESWL in children.

Keywords: Acute Kidney Injury, ESWL, Children

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INTRODUCTION

Urolithiasis affects almost 2%-3% of children and this age group has a high-risk for stone recurrence (6%-44%) (1, 2). ESWL is the preferred treatment for small upper urinary tract calculi in children, with well-known advantages such as high efficiency and ease of use on children (3). Despite the small ureteral diameter, fragments pass more easily because of the flexible structure in children (4).

ESWL consists of mechanical and dynamic effects for effective stone fragmentation. Cavitation bubble collapse is responsible for stone fragmentation, which can create destructive forces. Although many benefits are attributed to this treatment, there are risks associated with this procedure. ESWL may induce acute kidney injury (AKI) by causing harm to vessels and surrounding kidney tissues, inflammation, and hemodynamic impairment (5). Moreover, once renal injury resolves, persistent kidney damage may develop (6). There are published reports in the literature that these acute effects cause hemorrhaging, releasing some inflammatory cellular mediators. Animal studies have also proven the adverse effects of ESWL on kidneys (7).

Many studies continue to investigate how to best quantify the effect of acute kidney injury by evaluating various noninvasive biomarkers of renal injury (8). The current literature suggests that the most effective biomarkers of AKI are kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-D-glucosaminidase (NAG) and liver-type fatty acid binding protein (LFABP), which are expressed after ischemic and nephrotoxic AKI (8). KIM-1 is a type 1 transmembrane glycoprotein. Recent reports suggest that human and animal kidneys' proximal tubule epithelial cells express high levels of KIM-1 after ischemic or toxic injury (9, 10). NGAL is another potential AKI biomarker that may be able to identify early kidney injury. NAG is a lysosomal enzyme that it is abundantly expressed in proximal tubule epithelial cells (11). LFABP is a protein that

is normally expressed in the proximal tubules of the kidney and has been observed to be elevated in animal models of AKI(12). Various studies propose that KIM-1, NGAL, NAG, LFABP are promising biomarkers for diagnosing AKI and monitoring clinical improvement of the kidney (8). We aimed to evaluate AKI levels because they can help assess the amount of damage to the kidney after ESWL in children. It is the first study to evaluate AKI levels for ESWL treatment in the child age group.

MATERIALS AND METHODS

A prospective controlled study was performed between April and September 2013. This study was approved by the Institutional Review Board of the Dicle University Medical Faculty. All patients treated with ESWL gave their informed consent before the procedure. We also obtained informed consent from all other subjects preceding their participation in the study. We enrolled thirty consecutive child patients who underwent ESWL (Group1) with renal calculi less than 2cm. Subjects who had previous renal surgery, a solitary kidney, congenital renal anomalies, kidney stones in other side, or evidence of other urinary tract disorders such as pyelonephritis were excluded from the study.

Thirty control child patients (Group 2) were randomly chosen from patients' relatives. They had no known urogenital disease and no known history of urologic. Volunteers provided one freshly voided urine sample.

Patient demographic data was collected as age, sex, and stone size. Pre-operative tests, such as routine blood tests, serum biochemistry, urinalysis, urine culture, ultrasonography, and plain X-ray were recorded. Computerized tomography (CT) was done routinely in order to analyze the size and location of the stone as well as the anatomical structure. Pre-operative antibiotics were administered based on the results of the urine culture. Electrohydraulic extracorporeal lithotripter (Multimed Classic; Elmed, Ankara, Turkey) was used for ESWL. The power of the shock wave was started from the lowest level (14 kV) and could be elevated to the maximum

level (20 kV) until fragmentation was observed in fluoroscopy. Shock waves were administered until fragmentation was observed or a maximum of 1,000 waves per session for children younger than 5 years. For older children, they were administered until fragmentation or a maximum of 2,500 waves per session.

Patient urine creatinine levels and AKI levels were measured three times: before the first session of ESWL, two hours after the first session, and 24 hours after the first session. We used an auto analyzer, the Architect C16000 (Abbott Laboratories, Abbott Park, IL, USA). Urine NGAL, KIM-1, NAG, and L-FABP levels were determined using a commercially available quantitative sandwich immunoassay technique (SunRed Biotechnology Company, Shanghai, China). All activity of the enzymes tested were given as a ratio of biomarker to urine creatinine values for each patient.

Statistical analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 15 software (SPSS Inc., Chicago, USA). All the data are presented as mean and standard deviation $\pm$ SD. Values of data were compared with ANOVA analysis and $P < 0.05$ was considered significant.

RESULTS

Demographic data was comprised of patient group [(Group 1 ($n = 30$), 16 were male and 14 were female)] and a control group [(Group 2 ($n = 30$), 15 were male and 15 were female)]. The mean age of

patients was 7.9 ± 4.3 and 7.5 ± 2.4 years in group 1 and group 2, respectively ($p = 0.09$). The mean stone size was 88.1 ± 65.2 mm² in group 1. Demographic data was established and found to be similar between the two groups (table 1).

The mean levels of creatinine, KIM-1/Cr, NGAL/Cr, NAG/Cr, and LFABP/Cr are summarized in table 2, figure 1 and the statistical comparison of the levels is shown in table 3. The mean levels of KIM-1/Cr differ in the study group of pre-procedure patients when compared to those of the control ($p < 0.01$). Creatinine levels were similar between the two groups and were not statistically elevated after ESWL. KIM-1/Cr mean levels were presented for before ESWL, 2 hours after ESWL and 24 hours after ESWL were 1.13 ± 0.34 , 1.34 ± 0.78 , 2.72 ± 0.60 respectively. Twentyfour hours after procedure, KIM-1/Cr levels had increased significantly in urine compared to before ESWL levels ($p = 0.04$). The mean levels of NGAL/Cr were 535 ± 115 , 560 ± 141 , 544 ± 146 for the different operative time points. NGAL/Cr mean levels were not elevated significantly soon after ESWL, but there were significant differences between the study group patients and the control group patients 24 hours after procedure ($p < 0.01$). The mean levels of the NAG/Cr from before ESWL, 2 hours after ESWL and 24 hours after ESWL were 0.13 ± 0.03 , 0.17 ± 0.04 , 0.24 ± 0.02 respectively. The NAG/Cr levels for the study group were higher than control group values and increase significantly after the operation. The mean levels of LFABP /Cr levels were 0.33 ± 0.1 , 0.33 ± 0.12 , 0.27 ± 0.18 respectively, and did not change significantly after ESWL in urinary specimens (Figure1).

Table 1: Patient demographics and ESWL outcomes among groups

	Group 1 (n:30)	Group 2 (n:30)	p value
Age (yr)	7.9±4.3	7.5±2.4	0.09
Sex			
Male	16 (53%)	15 (50%)	
Female	14 (47%)	15 (50%)	
Side			
Right	18 (57%)		
Left	12 (42%)		
Stone size mm ²	88.1±65.2		
Mean HU	810±124.6		
Number of mean shock waves	2480 ± 860		
Mean energy level kV	19.2±6.92		

HU: Hounsfield units, ESWL: Extracorporeal shockwave lithotripsy

Table 2. Early renal injury markers in children with urolithiasis who underwent extracorporeal shock wave lithotripsy (ESWL)

	Controls (n=30)	Before ESWL (n=30)	After 2h ESWL (n=30)	After 24h ESWL (n=30)
Kim 1 /Cr	1.06 ± 0.24	1.13 ± 0.34	1.34± 0.78	2.72 ± 0.60
NGAL / Cr	370 ± 229	535 ± 115	560 ± 141	544 ± 146
LFABP / Cr	0.32 ± 0.27	0.33 ± 0.1	0.33 ± 0.12	0.27 ± 0.18
NAG / Cr	0.07 ± 0.01	0.13 ± 0.03	0.17 ± 0.04	0.24± 0.02

Table 3. Differences (p values) in the early kidney injury markers creatinine ratio between the first measurements and the controls.

Compared modalities	Kim 1 / Cr	NGAL / Cr	LFABP / Cr	NAG/Cr
Before ESWL/ After 2h ESWL	NS	NS	NS	<0.01
Before ESWL/ After 24h ESWL	0.04	NS	NS	<0.01
Before ESWL/ Controls	0.03	NS	NS	<0.01
After 24h ESWL/ Controls	<0.01	<0.01	NS	<0.01

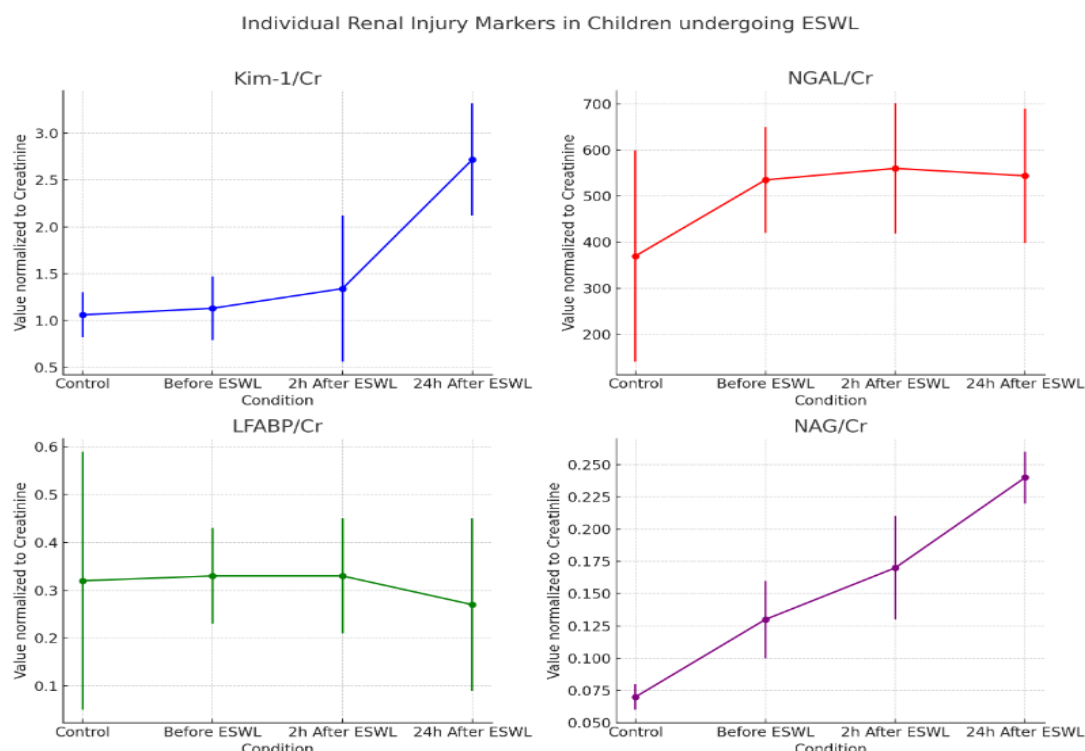


Figure1: Individual Renal Injury Markers in Children undergoing ESWL

DISCUSSION

ESWL is widely used for the management of stones located in the upper urinary tract. The safety, efficacy, and stone-free rates of ESWL have been shown in children (13, 14). Although this procedure is highly effective and safe, it is not completely free of side effects. Most of our knowledge about ESWL injury to the kidney is based on experimental animal studies where invasive methods were used to assess tissue damage (15). Morphological studies have shown that ESWL can rupture blood vessels and can damage the surrounding renal tubules in animals (15, 16). The acute effects of ESWL are defined in the literature (17). Acute trauma is usually localized in the area surrounding the stone. We encountered hematuria frequently in children after ESWL (13). In addition, there have been some published reports of severe acute injury of kidneys after ESWL, such as subcapsular or perineal bleeding (18). Although most hematomas resolve, some may cause life threatening hemodynamic instability and acute renal

failure (19). In the long term, animal and human studies have suggested that these acute hemorrhagic lesions may progress to scar formation and may lead to loss of kidney function (3, 15). Creatinine has been used for a long time to evaluate kidney damage, but it has been inadequate for early response. We aimed to determine the effect of ESWL on kidney damage in children and used potential AKI biomarkers levels as diagnostic indicators. Recently, several biomarkers have been explored for the early diagnosis of AKI, such as KIM-1, NGAL, NAG and LFABP (20). They are kidney-specific and highly sensitive for acute kidney injury. Furthermore, they are reliable and easily measurable in plasma or urine.

KIM-1 Kidney injury molecule 1 (KIM-1) has been found to be a sensitive marker of acute ischemic injury of the proximal tubular cells. It is excreted in

urine and thus has been used as a biomarker for AKI mostly in various types of kidney pathology (21). KIM-1 is a type I transmembrane glycoprotein. It has been shown that it is markedly upregulated in ischemic rat kidneys (9). Previous studies have shown KIM-1 levels were significantly higher in patients with ischemic acute tubular necrosis compared to levels in patients with other forms of acute renal failure (21). Another study demonstrated that levels of KIM-1 were associated with the severity of kidney injury (22). Authors found a positive correlation between the degree of scarring and KIM-1 levels in patients diagnosed with vesicoureteral reflux (23). Patients had significantly increased KIM-1 and NAG levels after ESWL when compared to their pre-procedure baseline levels. Urinary markers returned back to baseline levels within 2 weeks following ESWL (24). In our study we observed significantly higher levels of the KIM-1/Cr and NAG/Cr 24 hours after surgery. The results of the control group and pre-operative values of patients with kidney stones were similar for KIM-1/Cr, but NAG/Cr 24 levels were significantly higher in the study group than in the control group.

NGAL is a protein member of the lipocalin family, expressed by neutrophils and epithelial cells including proximal tubule cells. It has been identified as one of the fastest upregulated genes in the early phase of the post-ischemic animal kidney (25, 26). However, patients who did not experience AKI also displayed a significant increase in urine NGAL in the early postoperative period, although to a much lesser degree than those who subsequently developed AKI. Patients' NGAL/Cr values did not change significantly after operation, but control group levels were significantly lower than post-operative 24 hour levels.

L-FABP is a protein expressed in the proximal tubule of the kidney, filtered via the glomerulus and reabsorbed in the proximal tubules. Increased expression and urinary excretion have been described in animal models after renal tissue injury (27, 28). In patients with septic shock and AKI, urinary L-FABP measured at admission was

significantly higher in the control group than in the survivors (29). In our study, L-FABP/Cr value was found to be stable in urine for extended periods of time, and did not change urinary levels significantly.

NAG is a lysosomal enzyme that actively indicates damage to tubular cells in the kidney (30). Increased urinary NAG excretion has been reported in acute renal disease of varying etiology, primarily induced by cardiac surgery and renal transplantation (31). Chronic glomerular diseases limit the utility of NAG because urinary excretion of the enzyme is also elevated (30). Pre-operative NAG/Cr levels of group 1 patients were higher than the control group, plus the post-operative 2 hour and 24 hour levels also showed significant increases compared to pre-operative levels. We found NAG/Cr levels to be more sensitive than other biomarkers.

In our study, levels of AKI markers split to levels of creatinine for diminished effects of volume change. According to the results of our study, the pre-operative KIM-1 and NAG/Cr levels were observed to be significantly higher than the healthy volunteer patients, and they were more sensitive to detect damage to the kidney. The Kim-1/Cr and NAG/Cr values showed a significant increase in the first 24 hours after surgery.

Conventional imaging techniques or creatinine levels alone are not enough to rule out potentially significant injury to ESWL treated kidneys. In our study it was not changed in 24 hours after ESWL. We need to find a noninvasive diagnostic test that can reliably identify kidney injuries, especially in certain populations such as children, patients with renal disease or those undergoing multiple ESWL treatments. We had limitations in our study: patients numbers were low and we should have had longer patient follow-up to see when they start to fall back to preoperative levels. It is important to record ESWL shock wave numbers and kV for each child. After the first session of ESWL, we should adjust our treatment accordingly.

CONCLUSION

ESWL is safe and curative for urolithiasis in children, but there is no doubt that ESWL can lead to acute kidney injury. We aimed to determine the effect of ESWL on kidney damage and used potential AKI biomarkers levels as diagnostic indicators. In the future, we hope to use these biomarkers to evaluate ESWL's effect on kidney tissue after each session. Our data suggests that increased NAG/Cr and KIM 1/Cr levels may be one of the initial indicators of AKI after ESWL in children.

Conflict of interest: All the authors declare that there is no conflict of interest with any financial organization.

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