

## Short-term changes in renal function in children and adolescents undergoing extracorporeal shock wave lithotripsy

Emir Milišić<sup>1,2</sup>, Zlatan Zvizdić<sup>1</sup>, Asmir Jonuzi<sup>1</sup>, Edin Begić<sup>3,4</sup>, Lejla Milišić<sup>5</sup>, Amira Mešić<sup>6</sup>

<sup>1</sup>Clinic of Paediatric Surgery, Clinical Centre University of Sarajevo, <sup>2</sup>Department of Surgery, School of Medicine, Sarajevo School of Science and Technology, <sup>3</sup>Department of Cardiology, General Hospital "Prim. dr. Abdulah Nakaš", <sup>4</sup>Department of Pharmacology, School of Medicine, Sarajevo School of Science and Technology, <sup>5</sup>Clinic of Radiology, <sup>6</sup>Clinic of Anaesthesiology; Clinical Centre of the University of Sarajevo; Sarajevo, Bosnia and Herzegovina

### ABSTRACT

**Aim** To identify short-term effects of extracorporeal shock wave lithotripsy (ESWL) on renal function in children and adolescents with single kidney stones.

**Methods** In a 4-year period 30 children (15 boys and 15 girls) from 10 to 18 years of age were treated for unilateral renal stones with ESWL. Inclusion criteria were: up to 18 years of age, kidney stone (from 4 to 20 mm in diameter) visible on X-ray, first ESWL treatment, unilateral lithotripsy treatment without previous kidney surgery, patients without infravesical obstruction, patients without proven urinary infection, repeated use of one (the same) analgesic, patients without anticoagulant and antihypertensive therapy, patients without use of nephrotoxic drugs prior to and during the treatment, normal blood pressure, non-pregnancy patients with normal renal function. Serum enzymes (alkaline phosphatase, lactate dehydrogenase), cystatin C, serum and urine electrolytes (sodium, potassium, chloride), and urine neutrophil gelatinase-associated lipocalin (uNGAL) were tested before, on the first and fifth day after the treatment.

**Results** An increase of alkaline phosphatase and lactate dehydrogenase was statistically significant on day 1 ( $p < 0.05$ ) and values returned to normal on day 5. Serum cystatin C level was also significantly increased during the first four days after ESWL treatment ( $p < 0.05$ ) and returned to baseline on post-treatment day 5. There was a statistically significant difference in the level of uNGAL in urine before and 24 hours after ESWL treatment ( $p < 0.05$ ).

**Conclusion** The ESWL is a safe and curative procedure for the treatment of kidney stones in children and adolescents with no evidence of serious adverse effects on renal function.

**Key words:** electrolytes, lithotripsy, urolithiasis

### Corresponding author:

Emir Milišić

Clinic of Paediatric Surgery, Clinical Centre of the University of Sarajevo  
Bolnička 25, 71000 Sarajevo,  
Bosnia and Herzegovina

Phone: +387 33 297 394;

Fax: + 387 33 250 334;

E-mail: emirilejla@gmail.com

ORCID ID: <https://orcid.org/0000-0002-0927-3369>

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## INTRODUCTION

Imbalance between the crystallization promoters and the inhibitors causes a formation of deposits in the urinary tract known as urolithiasis (1). Urolithiasis occurs in 0.5%-15% of adults (2) and in 0.1%-5.5% of children (3). Due to the high rate of recurrence and significant health implications for the affected patients, urolithiasis requires immediate and adequate treatment. In the past, open surgical treatment was the primary treatment for urolithiasis but nowadays it accounts for only 1%-5.4% of surgical techniques (4,5,6). Recent advances in the endoscopic management of urolithiasis, in the form of ureteroscopy, percutaneous nephrolithotomy (PCNL) and laparoscopy, promoted rapid decrease of using surgical approach. Currently, extracorporeal shock wave lithotripsy (ESWL) is an effective first-line treatment modality and most widely used method of urolithiasis management in both adults and children (7). However, there are no generally harmonized guidelines for ESWL in children mainly due to necessary extended monitoring of its effectiveness and morbidity (8). Although generally considered as a minimally invasive treatment of urolithiasis, potential adverse effects of ESWL to renal parenchyma are still carefully evaluated mainly due to the fact that kidneys are exposed to high levels of energy during the treatment. With technological advancements in the design of shock wave lithotripsy, reduced requirements for general anaesthesia, hospital stay and reduced radiation exposure due to better fluoroscopic targeting, and considering acceptable success rates, a high safety profile and minimal morbidity, ESWL has become usual first-line treatment for paediatric urolithiasis (9,10). Before performing ESWL in children with urolithiasis, it is mandatory to carry out a complete metabolic evaluation and urinary tract imaging to exclude congenital anomalies such as ureteropelvic junction (UPJ) obstruction and obstructive megaureter. Indications for paediatric ESWL are similar to those for adults and consist of pain, haematuria, infection, obstruction or potential obstruction (11,12). There is a limited number of reports in literature about the short-term and long-term adverse effects of ESWL on kidney and its function (clinical and animal studies have shown complications ranging from self-limited haematuria to perinephric/nephric hematomas (13-17). In the past

decades, the glomerular filtration rate (GFR) has been widely assessed by measuring concentration of endogenous serum markers such as blood urea nitrogen and serum creatinine, but these endogenous markers proved inadequate in certain clinical settings. Also, the most widely used serum creatinine as index of renal function has not proved to be the most accurate marker of acute kidney injury (AKI) due to the fact that creatine is the primary marker of glomerular filtration and is not reliable in diagnosis of renal tubular injury (18). Furthermore, serum creatinine increases only after half of kidney function is lost, and is mostly presented after several days following acute renal insult (19).

According to the data, there are still no consistent reliable biomarkers in the detection of acute kidney injury (AKI) caused by ESWL treatment of urolithiasis. According to the data, there are still no consistent reliable biomarkers in detection of acute kidney injury (AKI) caused by ESWL treatment of urolithiasis.

The aim of this study was to evaluate safety and effects of ESWL regarding enzyme and electrolytes level in renal stone patients by measuring the level of serum enzymes alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum electrolytes, serum Cystatin C, and urine neutrophil gelatinase-associated lipocalin (uNGAL) before and after ESWL, as well as shockwave induced renal damage.

## PATIENTS AND METHODS

### Patients and study design

This prospective study was performed on children and adolescents who underwent ESWL monotherapy for urolithiasis from January 2012 to December 2015 on the Clinic of Paediatric Surgery, Clinical Centre of the University of Sarajevo. Thirty children (15 boys and 15 girls) aged 10 to 18 were selected for the study according to inclusion criteria. All patients (and their parents) were questioned about the onset of clinical symptoms of urolithiasis, the patient's history of previous diseases and treatment, history of urolithiasis among family members, history of urinary tract infections and diet.

Criteria for inclusion in the study group were children and adolescents of both genders up to 18 years of age, with kidney stone (pyelon, upper or

middle calyx, maximum 20 mm in diameter), visible on X-ray, first ESWL treatment (new cases), unilateral lithotripsy treatment without previous kidney surgery, without infravesical obstruction, without proven urinary infection, repeated use of one (the same) analgesic, without anticoagulant therapy, without antihypertensive therapy, without use of nephrotoxic drugs prior to and during the treatment, normal blood pressure, non-pregnancy, patients with normal renal function.

Exclusion criteria were kidney stone larger than 20 mm in diameter, acute urinary infection and systemic inflammation, urinary tract obstructions causing hydronephrosis, patients with congenital kidney or ureter anomalies, bilateral ESWL treatment, recurrent cases of urolithiasis, ureteral stones, patients with serum creatinine >350  $\mu\text{mol/L}$  over the past three months, hypertension, taking antihypertensive medicines, diabetes mellitus, previous surgeries on kidney, pregnancy, patients with impaired renal function, failure to sign informed consent.

Within 48 hours prior to the ESWL treatment, 1 and 5 days following treatment blood tests (leukocytes, sedimentation, C-reactive protein, sodium (Na), potassium (K), chloride (Cl), alkaline phosphatase (ALT), lactate dehydrogenase (LDH), cystatin C) were performed. Also, urinalysis (urine sediment and neutrophil gelatin-associated lipocalin (NGAL)) and urine culture were performed for all patients. In cases of positive laboratory findings for infection in serum and urine, patients were excluded from the study.

Blood pressure was measured for all patients and their urogenital system clinically evaluated.

ESWL treatment was indicated for stones from 4 to 20 mm in diameter. Following ESWL treatment, ultrasonography and/or X-ray of urinary tract was used for follow-up. An informed consent was obtained from all patients following an explanation of the purpose of the study. Ethical approval was obtained from Ethical Committee of Clinical Centre of the University of Sarajevo.

## Methods

The level of serum and urine enzymes was assayed according to the instructions provided with the corresponding enzymatic kits. Neutrophil gelatinase-associated lipocalin in urine (uNGAL) was

determined using chemiluminescent microparticle immunoassay (CMIA) (ARCHITECT i2000SR Immunoassay Analyzer, Abbot, USA).

An ESWL session took approximately 30 minutes and focused on the stone in a supine position. All patients who underwent ESWL treatment were sedated with the following medicinal products: atropine 0.01 mg/kg, fentanyl 1  $\mu\text{g/kg}$ , midazolam 0.5 mg/kg, ketamine 2 mg/kg. All medicines were given intravenously. The ESWL was performed with the Dornier HM-4 lithotripter (Dornier Medical Systems, Munich, Germany). The power was increased from 6 to 22 kV using a standardized protocol (500 shock waves up to 10 kV, 500 up to 14 kV, 1000 up to 18 kV, and 500 up to 22 kV) with the frequency of 60 shocks/min. The session was stopped when the machine's upper limit of shock waves per session (2500) was reached. The mean number of shocks was 1.000-2.500 waves per session and the pulse frequency was 70 shocks per minute.

## Statistical analysis

Mean ( $\pm$  standard deviation) values of data were calculated. All the data were presented as  $\pm$ SD. The mean values obtained before and at each of the tests following ESWL treatment were compared statistically by the 2-tailed Wilcoxon signed-rank test. The statistical level of 95% ( $p < 0.05$ ) was taken as significant for all performed tests.

## RESULTS

The study included 30 patients (15 males and 15 females). The mean age of patients was  $14 \pm 4.2$  years (range from 10 to 18 years). Of the patients included in the study, 16 (53.3%) had right-renal stones, 14 (46.7%) left-renal stones. There were no patients with bilateral stones. The mean size of the stones was  $9.56 \pm 4.21$  mm. The mean number of ESWL sessions was 2.03 (range from 1 to 6).

The most common type of stones both in female and male patients was calcium type. From the total of 24 calcium stones, 13 (39%) were presented in female and 11 (33%) in male patients. Infectious type of stone (struvite, carbon apatite) was found in one (3%) of females and in two (6%) males. Other stones (uric acid stones, cysteine) were less presented in three (9%) cases of both genders.

Regarding electrolytes, results showed (Table 1) significant ( $p < 0.01$ ) increase in serum levels of sodium, potassium, and chloride on 1<sup>st</sup> post-ESWL

**Table 1. Results of analysed serum electrolytes in patients with extracorporeal shock wave lithotripsy (ESWL)**

Parameter	Serum				Urine			
	Pre-ESWL (n=30)	Post-ESWL (mean + SD) (p) (n=30)			Pre-ESWL (n=30)	Post-ESWL (mean + SD) (p) (n=30)		
		1st Day	5th Day	D5-D1		1st Day	5th Day	D5-D1
Na <sup>+</sup> (m Eq/L)	140.3± 0.5	142.8±0.7; (0.001)*	137.1±0.6; (0.001) †	5.7± 0.7; (<0.001) ‡	164.9±1.09	171.0± 1.5; (<0.001)*	162.1± 1.2; (<0.001)†	8.9± 1.2; (<0.001)‡
K <sup>+</sup> (m Eq/L)	3.96± 0.07	4.1± 0.08 (<0.001)*	3.65± 0.08; (0.001) †	0.46±0.08; (<0.001)‡	14.98±0.5	16.1± 0.6; (<0.001)*	14.0±0.4; (<0.001) †	2.3±0.3; (<0.001)‡
Cl (m Eq/L)	102.5± 0.4	103.4± 0.5 (<0.001)*	99.3±0.6; (<0.001)†	4.13±0.5; (<0.001)‡	129.8± 1.4	134.0±1.4; (<0.001)*	128.0±1.4; (<0.001)†	5.97±0.6; (<0.001)‡

D5-D1 - ratio between values of electrolyte 120 (D5) and 24 (D1) hours after ESWL; \*pre-ESWL compared to day 1 post ESWL; †pre-ESWL compared to day 5 post ESWL; ‡day 1 compared to -day 5 post ESWL

day which gradually returned to pre-treatment value until the end of 5<sup>th</sup> post-ESWL day. Also, a significant ( $p<0.001$ ) increase in urinary sodium, potassium, and chloride excretion on 1<sup>st</sup> post-ESWL day was observed, with gradual return to pre-treatment value on 5<sup>th</sup> post- ESWL day.

*Serum enzyme analysis* (ALP, LDH), and cystatin C in 30 patients with renal stones who were treated by ESWL showed that there was a significant reduction thereof from day 1 to day 5 post ESWL. Also, results showed a significant increase in ALP on day 5 compared to pre-treatment values and significant decrease in LDH and cystatin C values on day 5 compared to pre-treatment values (Table 2).

**Table 2. Results of analysed serum enzymes and cystatin C in patients treated with extracorporeal shock wave lithotripsy (ESWL)**

Parameter	Pre - ESWL (mean + SD) (p) (n=30)	ESWL Effect		
		Post - ESWL (n=30) (mean + SD) (p)		
		1st Day	5th Day	D5-D1
ALP (U/L)	159.6±9.4	190.2±10.3 (* $p<0.001$ )	161.5±8.8 († $p<0.001$ )	28.7±6.0 (* $p<0.001$ )
LDH (U/L)	363.1±10.2	403.0±8.7 (* $p<0.001$ )	354.7±10.0 († $p<0.001$ )	48.3±5.5 (* $p<0.001$ )
Cystatin C (mg/L)	1.1±0.3	1.7±0.4 ( $p<0.001$ )*	1.3±0.2 († $p=0.005$ )†	0.4±0.2 ( $p<0.001$ )‡

ALP, alkaline phosphatase; LDH, lactate dehydrogenase; D5-D1 - ratio between values of marker 120 (D5) and 24 (D1) hours after ESWL; \*pre-ESWL compared to day 1 post ESWL; †pre-ESWL compared to day 5 post ESWL; ‡day 1 compared to day 5 post ESWL

Urinary NGAL level significantly decreased from day 1 to day 5 post ESWL, but it was significantly higher compared to the pre-treatment level (Table 3).

**Table 3. Urinary neutrophil gelatinase-associated lipocalin (NGAL) values in patients with extracorporeal shock wave lithotripsy (ESWL)**

Parameter	Pre - ESWL (mean + SD) (p) (n=30)	ESWL Effect		
		Post - ESWL (n=30) (mean + SD) (p)		
		1st Day	5th Day	D5-D1
Urinary NGAL (ng/ mL)	19.2±6.4	190.2±10.3 ( $p<0.001$ )*	61.5±8.8 († $p<0.001$ ) †	128.7±1.52 ( $p<0.001$ )‡

D5-D1 - ratio between values of urinary NGAL (D5) and 24 (D1) hours after ESWL; \*pre-ESWL compared to day 1 post ESWL; †pre-ESWL compared to day 5 post ESWL; ‡day 1 compared to day 5 post ESWL

## DISCUSSION

Among many clinical studies that identified ESWL short-term effects on renal function, Karlsson et al. in their study conducted in 1991 concluded that changes in renal function after ESWL treatment were moderate and all returned to normal after 4-5 days (20). Also, Karlsson et al. found no significant differences between values of GFR, serum creatinine, sodium and potassium levels prior and post ESWL (20). Unlike Karlsson et al. our results showed significantly higher sodium, potassium and chloride values on day 1 compared to day 5 post ESWL. Moreover, although this study showed significantly different sodium, potassium and chloride values on three observation points (pre ESWL, day 1 and day 5 post ESWL), it is of little relevance since they remained within reference values. A study conducted in Hungary has evaluated the safety of ESWL in children based on the measurement of blood parameters (sodium, potassium, urea, creatinine and C-reactive protein), urinary electrolytes (sodium, potassium and creatinine), urinary enzyme activity (aspartate transaminase, alanine transferase, alkaline phosphatase and lactate dehydrogenase) and the excretion of beta 2-microglobulin (21) and found

that ESWL induced only transient functional damage of tubular function in children (21). Comparison of serum enzymes ALP and LDH levels before and after ESWL treatment in this study showed the greatest increase of ALP and LDH on the 1<sup>st</sup> post-ESWL day, which returned to normal on the 5<sup>th</sup> post-ESWL day. However, no pre or post ESWL differences were found in serum and urinary levels of sodium, potassium and chloride. This matches results of studies analysing levels of serum enzymes and electrolytes in patients before and after ESWL (20-22).

Over time many biomarkers have been analysed for reliability and accuracy, usually including kidney injury molecule-1 (KIM-1), N-acetyl-Beta-D-glucosaminidase, NGAL, cystatin C, and interleukin-18. The current guidelines for the Acute Dialysis Quality Initiative (ADQI) recommended the integration of only cystatin C and NGAL into clinical practice (23).

One of the most promising early biomarkers for AKI in different clinical situations, in both adult and paediatric population is NGAL, also known as neutrophil glucosaminidase-associated lipocalin (24-27). The NGAL is a secretory protein that belongs to the family of lipocalins, present in diverse cells of the body: neutrophils, monocytes/ macrophages, adipocytes and epithelial cells (lungs, bowel, prostate, kidney, etc.) (23,24). Normal presence of NGAL in human tissues is in low concentration whereas a significant increase in serum and urine suggest various pathologic conditions. More recently, it was shown that urinalysis is more specific and urinary NGAL is more sensitive for early detection of AKI (28), especially using chemiluminescent microparticle immunoassay (CMIA), known as the ARCHITECT Urine NGAL assay (29). The NGAL excretion in urine only takes place when a proximal tubal damage disrupts NGAL reabsorption or increases NGAL synthesis. Fahmy et al. evaluated potential renal tubal damage in 50 patients with renal stones after ESWL treatment by determining the concentration of NGAL in voided urine before and on the first and fifth day after the procedure, and found that mean NGAL values were significantly increased post-ESWL and returned to baseline within 2 weeks post-ESWL (30). Also, Vittori et al. found that urinary NGAL levels increased soon after ESWL (3 hours) and quickly returned to and maintained baseline levels

(1-30 days post-ESWL) (31). They concluded that NGAL could be used as an early biomarker of renal damage. This is consistent with the results of our study since it showed a significant increase in the concentration of NGAL in urine on the first post-ESWL day compared to baseline values prior to ESWL with a gradual decline in the concentration over time so that the NGAL concentration on the fifth post ESWL day was for two-thirds lower than in the first post-ESWL day. Unfortunately, due to excessive costs to our institution, we were not able to analyse urinary NGAL concentration 2 weeks or a month following the treatment, while other studies showed return of urinary NGAL concentration to baseline values (31). Increased excretion of uNGAL was likely to occur due to an immediate trauma of the renal parenchyma, interstitial edema and ischemia, to which the epithelial tubular cells are extremely susceptible (31). Conversely, Kardakos et al. found no statistically significant differences in the levels of NGAL in serum and urine before and after ESWL (32) suggesting that during the application of the shock wave used in ESWL method, there was no acute injury to renal parenchyma (32).

Serum cystatin C (CysC) is another useful biomarker of renal function. CystC is a protease inhibitor produced by almost all human cells in a constant rate, freely filtrated, not secreted and not reabsorbed into to the blood stream (33). For that reason, changes in CystC serum level should be directly proportional to changes in glomerular filtration rate (GFR) (33). Numerous studies have shown that estimated GFR based on CystC is considered significantly more precise than other biomarkers (34). Salah et al. evaluated effect of ESWL on kidney function by measuring CystC before and after ESWL treatment on 50 patients with unilateral renal stone and found a rapid increase in serum CystC concentration after ESWL (35). Similar findings were reported by Nomikos and al. noting that the highest concentration of CystC was 6 hours after ESWL (36); they found elevated concentrations of CystC on the tenth day following ESWL treatment (35-37). This is consistent with the results of our study that showed mean value of cystatin C being significantly increased on the first day following ESWL with a gradual value reduction throughout the post-ESWL period. This study showed significantly different sodium, potassium and chloride

values on three observation points (pre ESWL, day 1 and day 5 post ESWL), but it is of little relevance since they remained within reference values; also, mean values of cystatin C were significantly increased on the first day following ESWL with gradual value reduction throughout the post-ESWL period as well as a significant increase in the concentration of NGAL in urine on the first post-ESWL day compared to baseline values prior to ESWL with a gradual decline in the concentration over time.

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In conclusion, further studies including larger population with the analysis of uNGAL concentration after 2 weeks and a month following the treatment should be performed to confirm whether values will return to baseline.

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## TRANSPARENCY DECLARATION

Competing interests: None to declare.

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