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RENAL ADVERSE EFFECTS OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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SUMMARY – Extracorporeal shockwave lithotripsy is not a novel therapeutic method in the treatment of urolithiasis. It uses shock waves (SW) created in the generator outside of the body that are then focused and directed on the calculus in the patient's body. It is the method of choice for the treatment of kidney stones smaller than 20 mm, and those in the proximal part of the ureter (up to 10 mm). Complications are relatively rare and most often clinically insignificant. SW can reversibly damage all parts of the renal parenchyma. The degree of damage depends on the number of SW and the energy level delivered to a particular tissue. Such changes are most often asymptomatic. Microhaematuria is present in virtually all patients, and macrohaematuria occurs in about 1/3 of patients. A rare but serious complication is a kidney rupture that requires surgical care that can sometimes lead to a nephrectomy. The occurrence of perinephric or subcapsular hematoma is rare and usually requires only conservative therapy. Despite the aforementioned negative impact of SW on the renal parenchyma (primarily around the calculus), studies have not shown that treatment with this method leads to significant renal function impairment in either the adult or paediatric population.

Key words: *Extracorporeal shockwave lithotripsy; Nephrolithiasis; Renal injury; Renal function*

Introduction

Urolithiasis is a significant health problem as its incidence is from 1 to 20% in adults and from 0.1 to 5.5% in children^{1,2}. Over the last few decades, the incidence of urinary stones has increased worldwide for all sex, age, and race groups. This has been linked to dietary changes, obesity, and also climate change. According to steadily increasing incidence, we can expect it to be a climate-related disease by the end of the century³.

Extracorporeal shockwave lithotripsy (ESWL) is a non-invasive, relatively safe, and highly effective treatment for urinary stones in appropriately selected patients, thus making it a very attractive method. It employs high energy acoustic waves (shock waves) outside the body to target and break stones within the

kidney and the ureter. The mechanism behind breakage is direct stress induced by the compressive positive pressure phase of the shock wave (SW) and cavitation, formation of the bubbles that erode the stone surface during the negative pressure phase⁴. ESWL can also be used in gastroenterology and orthopaedics.

Indication and contraindications for ESWL

ESWL is indicated for patients with symptomatic, uncomplicated kidney stones up to 20 mm in diameter and for stones of proximal ureter up to 10 mm. Larger kidney stones can be treated, but it is advised to insert a ureteral stent prior to the procedure to prevent obstruction with stone fragments and „stein strasse“ formation. Elimination of fragments is aggravated for stones located in the lower calyx, so the recommended diameter should not exceed 15 mm. Also, some types of stones do not respond well to ESWL, such as calcium oxalate monohydrate stones, brushite stones, and

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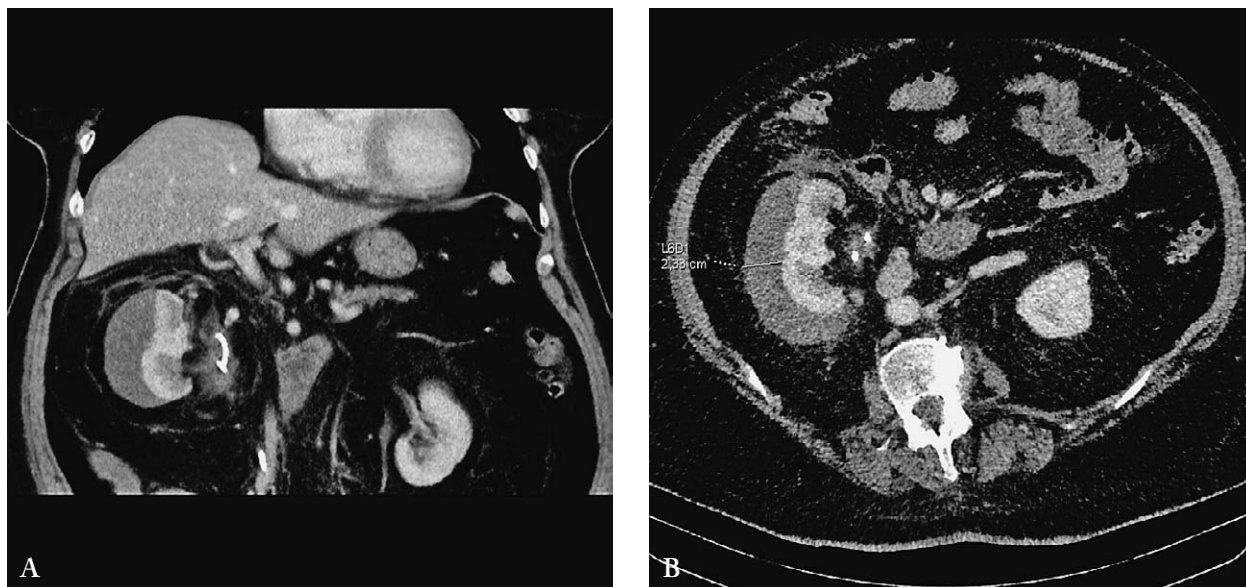


Fig. 1. CT scan of the large subcapsular renal hematoma after ESWL (1 day after treatment) performed for treatment of stone in the right kidney (A-frontal view, B-transverse view). With conservative therapy, three months after ESWL treatment, complete resolution of the hematoma was achieved.

a sub-type of cystine stones. In some cases, repeated treatments may be needed.

There are few absolute contraindications for ESWL and it should never be conducted in pregnant women and patients with an uncorrected coagulation disorder. Patients who have anatomical abnormalities of the urinary tract that could hinder fragment passage, such as ureteropelvic junction obstruction or ureteral stricture, should be excluded. Severe untreated hypertension is an excluding factor until the blood pressure is controlled, as it poses a greater risk of developing renal haemorrhage during the procedure. Active urinary tract infection is also a contraindication due to the risk of pyelonephritis or sepsis. Prior to the procedure, all patients should do a urine sampling for bacteriuria and pyuria, and in case of positive results, a urine culture and antibiotic treatment should be done⁵. Staghorn stones and large stones with a diameter over 20 mm are a relative contraindication. Also, aortic aneurysms and renal artery aneurysms are relative contraindications as they can result in life-threatening haemorrhage. Patients with skeletal deformities are not contraindicated, though it may be impossible to carry out ESWL. If the favourable SW path can be established, patients with skeletal deformities should not be excluded⁶.

In some patient groups, extra precautions should be taken during the procedure because of a greater risk of complications: patients with hypertension, diabetes mellitus, cardiovascular disease, reduced renal function, solitary kidney, in children and elderly patients. It is advised to closely monitor blood pressure and ECG during the treatment.

Complications of the procedure

Almost all patients who undergo ESWL experience microhaematuria and macrohaematuria occurs in about 1/3 of patients. Macrohaematuria is rarely severe, so in most cases does not require further medical interventions.

Incomplete stone fragmentation can lead to urinary tract obstruction if the fragments remain larger than 5 mm. Incomplete fragmentation is more common with stones of larger surface and harder composition (e.g. brushite stones). Obstruction of the upper urinary tract can cause flank pain and colic, hydronephrosis, acute kidney damage, alteration in glomerular filtration rate (GFR), and urinary tract infections. Placement of the internal stent or percutaneous nephrostomy may be needed to bypass the obstruction, depending on the stone size, kidney function parameters,

and patient's general state. If the obstruction does not resolve spontaneously, further ESWL or endoscopic procedures may be needed.

Damage to the renal tissue can affect all parenchymal components. The degree of damage is reciprocal to the level of energy and the number of SW delivered. Blood vessels are most commonly damaged, and as a result, subcapsular or perinephric haemorrhage with ipsilateral pain can happen, but irreversible acute renal failure was also described, most likely due to injury of glomerular corpuscles⁶. Subcapsular hematoma is a consequence of a ruptured large vessel in the renal capsule (Fig. 1). The incidence of hematomas ranges from 1% to 20%, depending on the variety of the lithotripter used for the procedure, radiological imaging method, and time of the assessment. The most important risk factor for developing hematomas is age, as incidence increases by double per decade, with untreated or uncorrected hypertension, diabetes mellitus, and generalized vascular calcification. Most hematomas resolve without any medical implication within weeks or months, without any long-term effects on the renal function, although, in some severe cases, they may result in lethal outcome^{4,7}.

Extrarenal damage to the other organs that has been described includes perforation of the colon, hepatic hematoma, rupture of the hepatic artery, acute necrotizing pancreatitis, rupture of the spleen, rupture of the abdominal aorta, dissecting abdominal wall abscess, iliac vein thrombosis, pneumothorax, urinothorax, among others.

Short-term effects on kidney function

Kidney injury is inevitable during every ESWL treatment and this process continues even when the procedure is finished. Effects of shock waves on kidney tissue can be distinguished into two major types: ischemic and traumatic vascular injury, and both of them have a different pathophysiological basis⁸⁻¹⁰. Traumatic injury is provoked by the sheer shock waves physical force. The ischemic (hypoxic) injury appears in both kidneys, not just the treated one, and is caused by renal vasoconstriction together with intraparenchymal bleeding. Oxidative stress mediated by ischemia-reperfusion might impart to kidney injury. In the last couple of years, a significant effort has been invested

into finding specific biomarkers sensitive enough to detect subclinical acute kidney injury, independently of GFR and diuresis. A number of biomarkers have been investigated: β 2-microglobulin, TNF- α , interleukins, N-acetyl-beta-D-glucosaminidase (NAG), urine neutrophil gelatinase-associated lipocalin (uNGAL), cystatin C and some others⁸⁻¹⁹.

Urinary β 2-microglobulin is a low molecular mass protein that is reabsorbed nearly by 100% in proximal tubules and therefore is a sensitive marker of proximal tubule cell damage^{11,12}. The increase of β 2-microglobulin in urine after ESWL results from tubular cell damage that reduces reabsorption capacity due to ischemic-reperfusion injury and oxidative stress^{10,13}. Nasseh et al. proved in a cross-sectional study on 91 patients with nephrolithiasis who underwent ESWL (power level 3, 2500 SW) that the urinary excretion of β 2-microglobulin increased by 167% immediately after treatment¹⁴. Li et al. performed a study on an animal model of rats that showed that β 2-microglobulin and IL-18 levels in urine stay significantly elevated even at 105 days post ESWL, as a consequence of inflammatory response to treatment¹⁵.

Interleukins take part in regulating immune response and inflammatory reactions, and interleukin-1 (IL-1) and interleukin-6 (IL-6) have been linked with post-ESWL renal injury¹⁶. Goktas et al. assessed the severity of the inflammatory response to ESWL in 35 patients by measuring the urinary excretion of IL-1 and IL-6. In the early post ESWL period, they observed a rise in IL-6 excretion compared to the control group, but after 14 days, the concentration decreased rapidly. On the contrary, IL-1 did not show statistically significant elevation, but after 14 days, its concentration increased. As so, IL-6 can be used as a biomarker of early renal inflammatory damage to ESWL and IL-1 as a late one¹⁶.

The NGAL is a secretory protein (lipocalins) present in the various cells (neutrophils, macrophages, epithelial cells of kidneys, lung, etc.). Normal presence in the tissue is low, so notable elevation in serum and urine suggests diverse pathological conditions. Fahmy et al. evaluated 50 patients after ESWL for potential tubular damage by measuring the concentration of NGAL in urine before and on the first and fifth day after the procedure. They found mean NGAL concentrations were markedly heightened post ESWL and returned to baseline values within 2 weeks¹⁷.

Cystatin C (CystC) is a protease inhibitor created by almost all cells in the human body at a steady rate, freely filtrated, not secreted or reabsorbed into the circulation. Because of that, CystC serum level is inversely proportional to alterations in glomerular filtration rate. Estimation of GFR based on CystC levels is more precise than other biomarkers². Salah et al. analysed the effect of ESWL on kidney function in 50 patients by measuring CystC before and after treatment and observed a fast rise in serum CystC concentration after the procedure¹⁸.

According to the data, there are still no consistent, reliable biomarkers in detecting acute kidney injury, and further studies involving urinary excretion of a broad variety of markers over a prolonged period of time are needed to predict and monitor potential long-term side effects. The current guidelines for the Acute Dialysis Quality Initiative (ADQI) advise the inclusion of only cystatin C and NGAL into the clinical practice¹⁹.

Long-term adverse effects

To date, the study that can fully and doubtlessly recognize the long-term effects of ESWL on kidneys and other bodily functions has not been conducted. Some studies have shown a greater risk of developing hypertension and diabetes mellitus.

A number of studies have proposed new-onset hypertension as a potential long-term complication of ESWL at a follow-up period from 90 days to 19 years. Some studies have confirmed the correlation, and some have disproven it²⁰⁻²⁴.

Krambeck et al. performed a study in the form of a questionnaire at a mean follow-up of 19 years. Of 578 patients who underwent ESWL treatment of kidney stones, 59% responded to the study. Results were matched up to a cohort of patients with kidney stones, who were treated conservatively, equalled for sex, age, and a year of onset, and they reported a significantly higher prevalence of hypertension in the ESWL group (odds ratio 1.47, 95% CI 1.03-2.10)²⁰.

A retrospective cohort study evaluated 4782 patients with nephrolithiasis who had no record of hypertension at presentation and 400 (8.4%) patients were treated with ESWL. The study followed the patients for an average of 9 years and by the results, ESWL therapy was not associated with an increased

risk of new-onset hypertension (adjusted hazard ratio 1.03)²¹.

Among researches that suggest new-onset hypertension, one prospective study by Janetschek et al. recognized age as a notable risk factor, with a rise in the internal resistive index in patients from 60 years of age and older²². Knapp et al. also recognized the increase in hypertension among older patients treated with ESWL²³. Transient hypertension has been recorded in patients that developed subcapsular hematomas as a complication of ESWL²⁴. Pathophysiological mechanisms behind long-term effects of ESWL have not yet been determined, although Banner et al. reported mesangial cell proliferation in animal models with pigs one month after ESWL²⁵.

As it is known that patients who suffer from urinary tract stones have a greater chance of developing hypertension, the relation with ESWL has to be carefully analysed. As the data is inconsistent, further, long term, prospective studies should be conducted^{7,26}.

Mayo Clinic did a retrospective 19-year follow-up study on 288 patients treated in 1985 with the HM3 lithotripter, which indicated that patients who underwent ESWL procedure had a greater chance to acquire diabetes mellitus than the control group (patients with kidney stones treated conservatively). This risk appeared to directly correlate with the number of shocks administered and the treatment intensity²⁰. A later study from the same centre pointed the disadvantages of the retrospective study, as the detection of diabetes was based on self-reporting questionnaires sent to all ESWL patients, with a concomitant Mayo Clinic medical record review to collect this data in the non-ESWL patients. This may have introduced a differential detection bias, particularly since controls may have been diagnosed with diabetes at other institutions. This study in a large, community-based cohort of stone formers did not suggest that receiving ESWL using an HM3 lithotripter increased the risk of diabetes²⁷.

As diabetes is a major life-altering possible complication, additional studies should be undertaken to evaluate the impact of ESWL on the pancreas and insulin secretion.

Few studies have correlated the formation of calcium phosphate stones (CaP) and brushite stones with a greater number of ESWL in the cohort²⁸. It seems that the greater number of procedures turns patients with calcium oxalate stones into patients with CaP

stones, and as the number of the procedures grows, patients with CaP stones turn to patients with brushite stones, which are far harder to eliminate with ESWL. Changes in stone composition are linked with injuries of renal papilla, leading to functional alteration of collecting ducts that result in the formation of crystalline deposits of apatite²⁹.

As ESWL plays a major role in the treatment of kidney stones in children, the possible long-term effects on kidneys were investigated in several studies³⁰. In all these studies, no long-term alterations of kidney function or the development of permanent renal scars were noticed³⁰.

Optimization of the procedure to minorize the adverse effects of ESWL

It is well recognized that the possibility and the severity of complications are directly connected to the number, firing rate, and energy level of SW⁴. That is why guidelines for safer ESWL treatment have been developed, but there is still no widely accepted protocol. The number of SW delivered during the treatment should range between 2000 and 4000⁷. Ideally, the procedure should be stopped immediately as the stone fragmentation is achieved. Usually, the SW rate in ESWL for urologic use is from 60 to 120 SW per minute, but studies have shown that lower rates (30 to 60 SW/min) are linked to both better stone fragmentation and reduced tissue injury^{31,32}. Stepwise increase of SW power – ramping – has several advantages. First, it is easier for patients to adapt to the discomfort of SW, it increases the chance of stone fragmentation, and shows a protective effect on kidney tissue³³.

Conclusion

ESWL has proven to be a safe and effective method from its implementation 30 years ago and is still a valuable treatment option for kidney and upper ureter stones in both children and adults. Although numerous side effects of SW have been described and studied, most of them are minor and can be minimized with adequate patient selection and procedure protocols. Long-term effects of ESWL on kidney function and overall health need further investigation as currently available data is inconclusive.

Conflict of interest: On behalf of both authors, the corresponding author states that there is no conflict of interest.

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Sažetak

UTJECAJ IZVANTJELESNOG MRVLJENJA KAMENACA ŠOKNIM VALOVIMA NA BUBREG

K. Smolić i D. Markić

Izvantjelesno mrvljenje kamenaca (ESWL) novija je terapijska metoda u liječenju urolitijaze. Temelji se na uporabi šok-valova koji se stvaraju u generatoru izvan tijela, fokusiraju i usmjeruju na kamenac u tijelu bolesnika. Metoda je izbora za liječenje bubrežnih kamenaca manjih od 20 mm te onih u proksimalnom dijelu mokraćovoda veličine do 10 mm. Komplikacije su relativno rijetke i najčešće klinički beznačajne. Šok valovi mogu reverzibilno oštetiti sve dijelove bubrežnog parenhima. Stupanj oštećenja ovisi o broju udaraca šok-valovima i energetske nivou koji je isporučen određenom tkivu. Takve promjene su najčešće asimptomatske. Mikrohematurija je prisutna praktički u svih bolesnika, a makrohaturija se javlja u oko 1/3 bolesnika. Rijetka, ali ozbiljna komplikacija je ruptura bubrega koja zahtijeva operacijsko zbrinjavanje i ponekada nefrektomiju. Pojava perinefritičnog ili subkapsularnog hematoma je rijetka i obično prolazi na konzervativnu terapiju. Unatoč prije spomenutom negativnom utjecaju šok valova na bubrežni parenhim (prvenstveno na onaj u okolici kamenca) studije nisu pokazale da liječenje ovom metodom dovodi do značajnijeg oštećenja bubrežne funkcije niti u odrasloj, niti u pedijatrijskoj populaciji.

Ključne riječi: Izvantjelesno mrvljenje kamenaca šoknim valovima; Nefrolitijaza; Bubrežno oštećenje; Bubrežna funkcija