Original Article – Urolithiasis
Grand J Urol 2023;3(3):113-20
DOI: 10.5505/GJU.2023.63325

Comparison of Fixed and Ramping Voltage Extracorporeal Shockwave Lithotripsy with Acute Kidney Injury Biomarkers: Prospective Randomized Clinical Study

Akut Böbrek Hasarı Biyobelirteçleri ile Sabit ve Artan Voltajlı Ekstrakorporeal Şok Dalga Litotripsinin Karşılaştırılması: Prospektif, Randomize Klinik Çalışma

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Cite as: Seker KG, Atar FA, Kural A, Turkay R, Yenice MG, Guner E, Sahin S, Tugcu V, Tasci AI. Comparison of fixed and ramping voltage extracorporeal shockwave lithotripsy with acute kidney injury biomarkers: Prospective randomized clinical study. Grand J Urol 2023;3(3):113-20

Submission date: 06 September 2023 **Acceptance date:** 16 September 2023 **Online first:** 18 September 2023 **Publication date:** 20 September 2023

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Abstract

Objective: To compare extracorporeal shock wave lithotripsy (ESWL) induced renal injury in patients undergoing different ESWL treatment protocols by measuring urinary tissue metalloproteinase-2 inhibitor (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) excretion.

Materials and Methods: This prospective, randomized study was conducted between April 2016 and June 2016 in group 1 patients undergoing fixed voltage ESWL and group 2 patients undergoing ramping voltage ESWL. Urinary TIMP-2 and IGFBP7 levels were analyzed before ESWL and 2 hours after ESWL, and urinary beta-2-microglobulin (β2-MG) and albumin were analyzed before ESWL and 1 week after ESWL to assess renal injury. The primary outcome was to compare the effect of ESWL on early renal injury with biochemical markers in the different treatment protocols, and the secondary outcome was to compare the two treatment protocols in terms of stone free rate and complications.

Results: There was no statistically significant difference between groups in terms of demographic and stone characteristics. There were statistically significant differences in serum creatinine and e-GFR at baseline and one week after treatment ($p<0.05$). There was no significant change in serum urea, urinary β2-MG and albumin levels before and after ESWL. There was a statistically significant increase in urinary TIMP-2, IGFBP7 and TIMP-2 x IGFBP7/1000 levels in both groups compared to baseline ($p<0.05$). There was no statistically significant difference in the rates of stone free and complications between the groups ($p>0.05$).

Conclusion: In this prospective randomized study, we observed a significant increase in TIMP-2, IGFBP7 and combination levels after ESWL treatment in both groups, suggesting that these two biomarkers could be used to identify acute kidney injury due to ESWL. However, the comprehensive evaluation of clinical parameters and urinary markers did not differ in the rates of renal injury, success, and complications after ESWL in both protocols.

Keywords: extracorporeal shock wave lithotripsy, urolithiasis, acute kidney injury, biomarker

Öz

Amaç: Ekstrakorporeal şok dalga litotripsi (ESWL) ile indüklenen böbrek hasarını, üriner doku metalloproteinaz-2 inhibitörü (TIMP-2) ve insülin benzeri büyüme faktörü bağlayıcı protein 7 (IGFBP7) atılımını ölçerek farklı ESWL tedavi protokolleri uygulanan hastalarda karşılaştırmak.

Gereçler ve Yöntem: Bu prospektif randomize çalışmaya Nisan 2016 - Haziran 2016 tarihleri arasında sabit voltaj ile ESWL uygulanan hastalar Grup 1, artan voltaj ile ESWL uygulanan hastalar ise Grup 2 olmak üzere toplamda 88 hasta alındı. ESWL'den önce ve 1 hafta sonra üriner beta-2 mikroglobulin (β2-MG) ve albumin, ESWL'den önce ve 2 saat sonra üriner TIMP-2 ve IGFBP7 düzeyleri böbrek hasarını değerlendirmek için analiz edildi. Birincil sonlanım noktası farklı tedavi protokollerinde ESWL'nin erken dönem böbrek hasarına etkisinin biyokimyasal belirteçlerle karşılaştırılması, ikincil sonlanım noktası ise iki farklı tedavi protokolünün taşsızlık oranı ve komplikasyonlar açısından karşılaştırılması olarak belirlendi.

Bulgular: Gruplar arasında demografik özellikler ve taş karakteristikleri açısından istatistiksel olarak anlamlı fark saptanmadı. Grup 1'in başlangıç ile bir hafta sonraki serum kreatinin ve e-GFR değerleri arasında istatistiksel olarak anlamlı bir fark saptandı. ($p<0.05$). ESWL'den önce ve sonra serum üre, idrar β2-MG ve albumin düzeylerinde anlamlı bir değişiklik izlenmedi. Her iki grupta da idrar TIMP-2, IGFBP7 ve TIMP-2 x IGFBP7/1000 düzeyleri başlangıca göre istatiksel olarak anlamlı bir artış gösterdi ($p<0.05$). Gruplar arasında taşsızlık ve komplikasyon oranları arasında istatiksel olarak anlamlı bir fark saptanmadı ($p>0.05$).

Sonuç: Bu prospektif, randomize çalışmada her iki grupta ESWL tedavisi sonrası TIMP- 2, IGFBP7 ve kombinasyon düzeylerinde anlamlı artış olduğunu izledik, bu durum ESWL'ye bağlı akut renal hasarın belirlenmesinde, bu iki biyobelirteçin kullanılabileceğini göstermiştir. Bununla birlikte klinik parametreler ve üriner belirteçlerin kapsamlı bir şekilde değerlendirilmesi, her iki protokolde ESWL sonrası böbrek hasarı, başarı ve komplikasyon oranlarında farklılık göstermemiştir.

Anahtar kelimeler: ekstrakorporeal şok dalgası litotripsi, ürolitiyazis, akut böbrek hasarı, biyobelirteç

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) has been used successfully for many years in the minimally invasive treatment of upper urinary tract stone disease. Although ESWL is considered a minimally invasive treatment, it has been shown to cause various short- and long-term structural and functional changes in the kidney. Short-term renal damage may be due to vascular or tubular mechanical trauma or oxidative stress due to free radical formation causing ischemia-reperfusion injury in the renal capillary system. ESWL may cause acute kidney injury (AKI) by causing peritubular vessel rupture, ischemia, hemorrhage, inflammation and hemodynamic disturbance [1,2].

Potential renal injury after ESWL has been studied using many biochemical parameters. Markers such as serum creatinine and lactate dehydrogenase have been studied in the blood, and markers such as microalbumin, albumin and β2-microglobulin (β2-MG) have been studied in the urine to indicate tubular damage [2]. However, there is no clear biomarker that can provide clinicians with an early and accurate indication of kidney injury following ESWL.

Recently, several new biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) have been studied in the detection of kidney injury after ESWL. Some of these biomarkers are indeed superior to others for early diagnosis. However, follow-up studies have shown that most of them are not specific for AKI [2,3].

In recent years, new potential biomarkers for the early detection of AKI have been identified. The most prominent are tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7). Both molecules have been shown to prevent renal tubular cell division in the G1 phase of the cell cycle by arresting the G1-S cell cycle in sepsis and ischemia. Because of all these proven effects, TIMP-2 and IGFBP7 are currently considered to be two promising biomarkers for the identification of AKI [3,4].

Several strategies with different treatment protocols have been used to improve the efficacy of ESWL in the treatment of urolithiasis and to minimise renal damage [5]. In porcine models, a stepwise increase in voltage has been shown to significantly reduce the size of renal parenchymal haemorrhagic lesions [6]. To date, clinical evidence in humans has only come from studies with small numbers of participants and/or suboptimal study design. Despite these negative factors, these studies suggest that stepwise ramping ESWL treatment is safe and may even provide a protective effect compared to conventional fixed voltage [7-9]. However, there are conflicting data regarding the effect of different voltage applications in ESWL treatment on clinical efficacy and complications [10-13].

In our study, urinary TIMP-2 and IGFBP7, which are used to determine AKI, are investigated for the first time in ESWL treatment. In our study, we aimed to compare the effect of ESWL treatment on AKI in patients undergoing ESWL in different treatment protocols using biomarkers of AKI and to compare these two treatment protocols in terms of success and complications.

Materials and Methods

Between April 2016 and June 2016, a total of 88 patients who underwent ESWL treatment for the first time with a diagnosis of kidney stones at Bakırköy Dr. Sadi Konuk Health Application and Research Centre were included in the study.

Patients were randomized into two groups: group 1: constant, conventional, fixed -voltage protocol and group 2: escalating, stepwise ramping voltage protocol using an online-based computer programme.

Inclusion criteria were: age older than 18 years, unilateral radiopaque kidney stones and no previous ESWL treatment. Exclusion criteria were: age younger than 18 years, bleeding tendency, positive urine culture, uncontrolled hypertension, use of nephrotoxic drugs, autoimmune disease, polycystic kidney disease, congenital renal malformations, musculoskeletal disorders, ureteral stent, or nephrostomy catheter. None of the patients in the study had obstruction below the level of the stone in the urinary tract, obstruction at the level of the stone or uremia.

After obtaining informed consent to participate in the study, complete blood count, biochemical parameters, coagulation test, serological tests and urine culture were prospectively evaluated for each patient before ESWL. All patients underwent radiological evaluation before and after ESWL by kidney ureter bladder (KUB) X-ray, urinary tract ultrasonography (USG) and non-contrast spiral computed tomography (CT). Stone size was calculated in millimeters based on the longest axis.

Routine biochemical tests including creatinine (mg/dL), urinary β2-MG (mg/L) and albumin (mg/dL) before and one week after ESWL in all patients, urinary TIMP-2 (ng/mL) and IGFBP7 (ng/mL) levels before and two hours after ESWL were prospectively analyzed to assess kidney injury. Estimated glomerular filtration rate (e-GFR) was calculated from serum creatinine levels using the Modification of Diet in Renal Disease Study Equation (MDRD) [14].

The degree of stone fragmentation at 3 months after ESWL was categorized by CT: stone-free, <2 mm, 2-5 mm and >5 mm in 4 groups. Success was defined as complete stone-free. All radiographic images were evaluated by the same radiologist and urologist to minimize interobserver variability. Clavien-Dindo classification was used in the evaluation of complications [15].

Both groups were compared in terms of demographic data [age, gender, body mass index (BMI)], stone characteristics [size, localization, Hounsfield unit (HU), stone skin distance (SSD)], ESWL treatment data (success and complication rates) and changes in serum and urinary biomarkers.

The primary endpoint of the study was to compare the effect of ESWL on early renal damage in different treatment protocols using biochemical markers, and the secondary endpoint was to compare two different treatment protocols in terms of stone-free rate and complications.

Ethical committee approval number 2016- 110 was obtained from Bakırköy Dr. Sadi Konuk Health Application and Research Centre, Ethical Committee. In addition, funding for this study was obtained from the Bakırköy Dr.Sadi Konuk Health Application and Research Centre Education Planning Board.

ESWL Protocol

Group 1 (constant, conventional, fixed) received 2000 shock

waves at 18 kilovolts (kV) energy, 1 Hz frequency, and group 2 (escalating, stepwise ramping) received a total of 2000 shock wave lithotripsy protocols at 1 Hz frequency, increased by 500 shock waves at 12-14-16-18 kV energy steps.

ESWL was performed in a single session in the supine position using a triple focus F3 (3.5 x 16 mm / 4.0 x 25 mm / 6.0 x 30 mm), piezoelectrolytic lithotripter, Wolf Piezolith- 3000 (Richard Wolf GmbH, Knittlingen, Germany). All ESWL treatments were performed by a single urologist. In most cases, a combination of ultrasound and fluoroscopy was used to target the stone.

Serum and Urine Analyses

Urine samples were immediately centrifuged at 2000 xg for 10 minutes. Aliquots of the urine supernatant were stored at -80°C for analysis. Urinary levels of TIMP-2 and IGFBP7 were assessed by ELISA. TIMP-2, IGFBP7 were analyzed using a human TIMP-2, IGFBP7 ELISA kit (YHB3004Hu, YHB3609 Hu, respectively) purchased from Shanghai Yehua Biological Technology (YHB, Shanghai, China) according to the manufacturer's instructions. Levels were expressed as ng/mL. The combination of TIMP-2 and IGFBP7 was expressed as TIMP-2 x IGFBP7/1000 and its level was expressed as ng^2/mL^2. The intra-assay coefficient of variation of TIMP-2 and IGFBP7 was 10% and 12% respectively. Urine β2-MG was analysed by particle-enhanced immunonephelometry using the BNII system. The upper limit of the reference range for urine is 0.2 mg/L.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analyses. In addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), the Student t test was used for between-group comparisons of normally distributed quantitative data, and the Mann-Whitney U test was used for comparisons of non-normally distributed variables. Paired-sample t-test was used for within-group comparisons of normally distributed parameters, and Wilcoxon signed-ranks test was used for within-group comparisons of non-normally distributed parameters. Pearson's chi-squared test, Fisher's Freeman-Halton test, Fisher's exact test and Yates' continuity correction test were used to compare qualitative data. Significance was assessed at the $p<0.05$ level.

Results

Of the 88 patients who participated in the study, 45.5% (n=40) were male and 54.5% (n=48) were female. The age of the patients ranged from 18 to 66 years with a mean age of 42.60±11.71 years. There was no statistically significant difference between the groups for age, gender and BMI measurements ($p>0.05$). No statistically significant difference was found between the groups regarding side, location, multiple stone status, stone size, stone density, SSD ($p>0.05$). Demographic data and stone characteristics are shown in **Table 1.**

In group 1, a statistically significant difference was found between creatinine and e-GFR measurements before ESWL and creatinine and e-GFR measurements after ESWL (p=0.001, p=0.001, $p<0.01$, respectively). In group 1, no statistically significant difference was found between urea, β2-MG and albumin measurements before ESWL and urea, β2-MG and albumin measurements after ESWL (p=0.455, p=0.317, p=0.414, respectively). In group 2, no statistically significant difference was found between creatinine, e-GFR, urea, β2-MG and albumin measurements before ESWL and creatinine, e-GFR, urea, β2-MG and albumin measurements after ESWL (p=0.053, p=0.074, p=0.781, p=0.564, p=0.074, respectively $p>0.05$). Data on the measurement of laboratory markers of the groups are shown in **Table 2** and **Table 3.**

In group 1, the difference of 1.26±2.49 units between IGFBP7 concentration measurements before ESWL and IGFBP7 concentration measurements after ESWL was statistically significant (p=0.001; $p<0.01$). In group 2, the difference of 1.07±1.95 units between IGFBP7 concentration measurements before ESWL and IGFBP-7 concentration measurements after ESWL was statistically significant (p=0.001; $p<0.01$). In group 1, the difference of 12.89±52.50 units between TIMP-2 concentration measurements before ESWL and TIMP-2

Table 1. Data on demographic characteristics and stone characteristics by groups

Group		Group 1 (n=44)	Group 2 (n=44)	P value
Age (years)	Min-Max (Median)	18-66 (47)	20-66 (43)	[a]0.257
	Mean±SD	44.02±12.83	41.18±10.42	
Gender; n (%)	Male	21 (47.7)	19 (43.2)	[b]0.830
	Female	23 (52.3)	25 (56.8)	
	Min-Max (Median)	19.1-44.4 (25.3)	19-27.8 (25.5)	
	Mean±SD	25.90±4.10	25.02±1.84	
Side; n (%)	Left	24 (54.5)	22 (50.0)	[b]0.831
	Right	20 (45.5)	22 (50.0)	
Location; n (%)	Pelvis	24 (54.5)	19 (43.2)	[c]0.426
	Upper	7 (15.9)	6 (13.6)	
	Middle	8 (18.2)	15 (34.1)	
	Lower	5 (11.4)	4 (9.1)	
Number of stones; n (%)	Single	40 (90.9)	35 (79.5)	[b]0.229
	Multiple	4 (9.1)	9 (20.5)	
Stone size; n (%)	<5 mm	1 (2.3)	4 (9.1)	[c]0.484
	5-10 mm	23 (52.3)	19 (43.2)	
	10-20 mm	18 (40.9)	20 (45.5)	
	>20 mm	2 (4.5)	1 (2.3)	
Stone density; n (%)	<1000 HU	27 (61.4)	23 (52.3)	[b]0.519
	>1000 HU	17 (38.6)	21 (47.7)	
SSD	Min-Max (Median)	4.4-14.4 (8.4)	6-15 (8.9)	[a]0.673
	Mean±SD	8.76±2.06	8.94±1.92	

[a]Student-t Test; [b]Yates' continuity correction test; [c]Fisher Freeman Halton test; SD: standart deviation; HU: Hounsfield unit; SSD: stone-to-skin distance

Table 2. Evaluations related to biochemical measurements according to groups

	Group 1 (n=44)	Group 2 (n=44)	P value
	Min-Max (Median)	**Min-Max (Median)**	
	Mean±SD	**Mean±SD**	
Creatinine before ESWL	0.4-1.1 (0.8)	0.5-1.1 (0.8)	[a]0.876
	0.78±0.18	0.77±0.16	
Creatinine after ESWL	0.5-1.2 (0.8)	0.4-1.3 (0.8)	[a]0.188
	0.85±0.19	0.80±0.19	
[e]p	**0.001****	0.053	
Urea before ESWL	14-96.3 (28)	15-45.9 (25.9)	[f]0.075
	29.82±12.98	25.66±6.29	
Urea after ESWL	18-85 (29.5)	14.8-52.6 (25)	**[f]0.011***
	30.38±10.91	25.64±7.54	
[g]p	0.455	0.781	
e-GFR before ESWL	60.5-149.3 (102.1)	73-129.8 (108.9)	[a]0.232
	103.70±17.30	107.68±13.41	
e-GFR after ESWL	51.9-146.8 (98.8)	7.9-135.8 (106.6)	[a]0.194
	97.51±19.50	103.11±20.61	
[e]p	**0.001****	0.074	
Albumin before ESWL	0.1-80 (4)	0-76.4 (2.1)	[f]0.409
	9.85±16.89	8.12±14.99	
Albumin after ESWL	0.2-54.7 (2.3)	0.1-17.1 (2.5)	[f]0.445
	7.56±12.23	4.20±4.53	
[g]p	0.414	0.074	

[a]Student-t Test; [e]Paired Samples t Test; [f]Mann-Whitney U Test; [g]Wilcoxon Signed Rank test; *p<0,05; **p<0,01; ESWL: extracorporeal shock wave lithotripsy; e-GFR: estimated glomerular filtration rate

Table 3. Evaluation of Beta-2 microglobulin (β2-MG) measurements according to groups

		Group 1 (n=44)	Group 2 (n=44)
		n (%)	n (%)
β2-MG before ESWL	**<0.21**	43 (97.7)	42 (95.5)
	>0.21	1 (2.3)	2 (4.5)
β2-MG after ESWL	**<0.21**	41 (93.2)	43 (97.7)
	>0.21	3 (6.8)	1 (2.3)
	[g]p	0.317	0.564

[g]Wilcoxon Signed Rank test; β2-MG: β2-microglobulin; ESWL: extracorporeal shock wave lithotripsy

concentration measurements after ESWL was statistically significant (p≤0.05). In group 2, the difference of 12.81±43.03 units between TIMP-2 concentration measurements before ESWL and TIMP-2 concentration measurements after ESWL was statistically significant (p=0.019; p<0.05).

In group 1, the difference of 0.12±0.31 units between TIMP-2xIGFBP7/1000 concentration measurements before ESWL and TIMP-2xIGFBP7/1000 concentration measurements after ESWL was statistically significant (p=0.001; p<0.01). In group 2, the difference of 0.15±0.27 units between TIMP-2xIGFBP7/1000 concentration measurements before ESWL and TIMP-2xIGFBP7/1000 concentration measurements after ESWL was statistically significant (p=0.001; p<0.01) (**Figure 1).** The results of IGFBP7, TIMP-2 and TIMP-2xIGFBP7/1000 concentration measurements by group are shown in **Table 4.**

When the complication and success rates of both groups were evaluated, no statistically significant difference was found (p: 1.000 and p: 0.606, respectively). The success rate of ESWL treatment was 81.8% in group 1 and 84.1% in group 2. Patients with residual stones underwent additional intervention or surgery. Complications were renal colic (grade 1) in 3 patients, hematuria (grade 1) in 1 patient, pyelonephritis (grade 2) in 1 patient and perirenal hematoma (grade 3a) in 1 patient in group 1. Complications in group 2 were renal colic (grade 1) in 2 patients, hematuria (grade 1) in 2 patients and urinary tract infection (grade 2) in 1 patient. There were no major complications. All complications were managed conservatively **(Table 5).**

Discussion

The mechanism of renal injury after ESWL is still not fully understood. The effects of a transient decrease in renal blood flow, oxidative stress due to the formation of free oxygen radicals resulting from ischemic damage, thermal and cavitation effects, and vascular damage have been implicated as mechanisms [16]. The development of ESWL treatment strategies that reduce or prevent tissue damage and the practical use of sensitive biomarkers that can show the damage that has occurred will help to determine renal damage after ESWL [17].

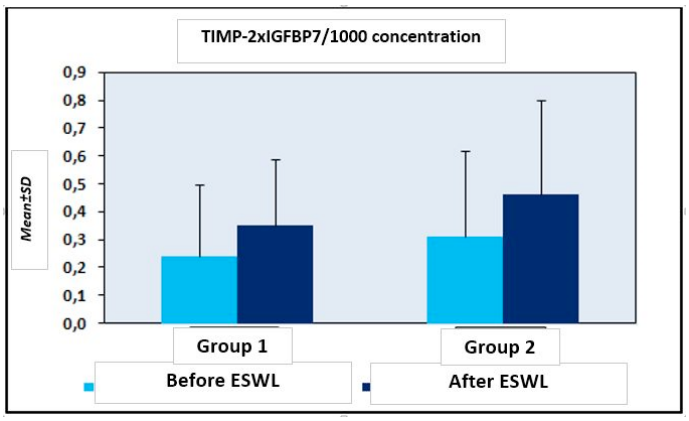

Figure 1. Distribution of TIMP-2 x IGFBP7 concentration measurements by groups

Table 4. Evaluation of IGFBP-7, TIMP-2 and TIMP-2xIGFBP7/1000 concentration measurements according to groups

	Group1 (n=44)	Group 2 (n=44)	P value
	Min-Max (Median)	**Min-Max (Median)**	
	Mean±SD	**Mean±SD**	
IGFBP7 Concentration before ESWL	0.2-10.8 (2.9)	0.4-12.1 (2.9)	[f]0.670
	3.20±2.09	3.71±2.80	
IGFBP7 Concentration after ESWL	0.4-9.3 (4.3)	0.5-12.8 (4.3)	[f]0.732
	4.46±2.10	4.78±2.64	
[g]p	**0.001****	**0.001****	
TIMP-2 Concentration before ESWL	0.8-211.8 (62.8)	0-168.8 (90.5)	[f]0.097
	65.28±48.13	78.04±46.07	
TIMP-2 Concentration after ESWL	0-203.2 (72.5)	8.5-189.4 (89.6)	[f]0.169
	78.18±48.64	90.85±48.33	
[g]p	**0.050***	**0.019***	
TIMP-2 x IGFBP7 /1000 Before ESWL	0-1.2 (0.2)	0-1.4 (0.3)	[f]0.313
	0.24±0.26	0.31±0.31	
TIMP-2 x IGFBP7 /1000 After ESWL	0-0.9 (0.3)	0-1.3 (0.4)	[f]0.187
	0.35±0.24	0.46±0.34	
[g]p	**0.001****	**0.001****	

[f]Mann-Whitney U test; [g]Wilcoxon Signed Rank test; *p≤0,05; **p<0,01; TIMP-2: Tissue inhibitor of metalloproteinase-2; IGFBP7: Insulin-like growth factor binding protein 7

Table 5. Data on complications and success results

Group 1 (n=44)		Group 2 (n=44)		P value
Complication; n (%)	**None**	38 (86.4)	39 (88.6)	[b]1.000
	Yes	6 (13.6)	5 (11.4)	
Rest stone size; n (%)	**None**	36 (81.8)	37 (84.1)	[c]0.605
	<2 mm	1 (2.3)	0 (0)	
	2-5 mm	6 (13.6)	4 (9.1)	
	>5mm	1 (2.3)	3 (6.8)	

[b]Yates' Continuity Correction test;
[c]Fisher Freeman Halton test

Urinary biomarkers have been widely used to assess kidney injury in various clinical settings and can provide earlier and more sensitive detection of kidney injury with good correlation to clinical outcomes. Recently, data have been reported from multicentre studies of the (TIMP2) x (IGFBP7) /1000 combination in critically ill patients. This combination has been validated for risk stratification of moderate to severe AKI associated with cell cycle arrest [18,19] A urine (TIMP2) x (IGFBP7) value >0.3 (ng/mL) ^{2}/1000 was found to have >90% sensitivity in predicting the development of moderate to severe AKI within 12 hours [19]. Unlike other new AKI biomarkers that reflect renal cell damage or impaired renal function, these markers are thought to reflect the renal tubular epithelial response [18,20]. (TIMP2) x (IGFBP7) compared to other markers such as NGAL, KIM-1, cystatin C and IL-18, it has been associated with superior results for AKI risk stratification [18]. Similar results were found in a study of patients undergoing cardiopulmonary bypass. Measurement of (TIMP-2) x (IGFBP-7) in urine proved to be a highly sensitive marker of AKI in cardiac surgery patients [21]. In contrast to all these positive data, in another study, in urine samples collected from 94 intensive care unit patients, these biomarkers did not differ between patients with and without AKI [22]. In a meta-analysis performed to evaluate the diagnostic accuracy of the urinary (TIMP-2) x (IGFBP7) combination for AKI in adult patients, it was concluded that the urinary (TIMP-2) x (IGFBP7) combination may be a reliable biomarker for the early detection of AKI [23]. In our study, we evaluated these two biomarkers and their combination in the assessment of AKI after ESWL at two hours after ESWL. According to our results, TIMP-2, IGFBP7 and their combination were statistically significantly increased in both groups after ESWL. Based on the data obtained, we believe that these biomarkers can be used to assess AKI after ESWL.

In addition to these new biomarkers, the study evaluated and confirmed the utility of known indicators of kidney function. The basic markers of serum creatinine, urea and e-GFR and urinary albuminuria, another way of assessing kidney damage, were assessed [2]. Serum creatinine and e-GFR levels were statistically significantly higher in group 1 than at baseline. However, it is well known that markers such as urea and creatinine used to monitor kidney function are not reliable enough to detect early kidney damage. However, all these methods are mainly useful for assessing chronic renal failure and show low sensitivity in acute injury processes. There are many studies in the literature evaluating e-GFR and serum creatinine levels before and after ESWL, and most of these studies did not find significant changes in GFR and serum creatinine levels.

In determining tubular damage after ESWL, the increase in urinary low-molecular-weight proteins and renal tubular enzymes other than albumin has also been studied. As β2-MG is one of the low molecular weight proteins and is completely filtered from the glomeruli, increased urinary excretion is observed in cases of proximal tubule dysfunction [24]. In their study investigating the effect of ESWL on renal tubular damage, Nasseh et al. reported that urinary β2-MG increased significantly immediately after ESWL. They also highlighted that the likelihood of this damage was higher in patients with hypertension and a history of previous ESWL compared to others [25]. Skuginna et al. found evidence that urinary β2-MG levels 24 hours after constant and stepwise voltage ramping ESWL were higher in the constant group than in the stepwise voltage ramping group, but the difference between

the changes was not statistically significant (p=0.06) [12]. Lambert et al. found no statistically significant difference between urinary biomarkers before and after treatment in the fixed and escalating voltage ESWL groups. However, they found a significant increase in β2-MG and microalbumin 1 week after ESWL and suggested that there may be less renal damage in the escalating voltage ESWL group [8]. In our study, no statistically significant difference was found between β2-MG levels in the two groups.

Although the safety and efficacy of ESWL have been demonstrated in large series studies, serious side effects and complications associated with ESWL can occur. Complications related to ESWL can be seen in acute and chronic periods. When the mechanism of complications is analyzed, they are directly related to shock waves, stone fragmentation, and the effects of stone fragments as they pass through the urinary system. Several studies have shown that ESWL causes acute or chronic renal damage [26]. Most of our knowledge about ESWL damage to the kidney is based on animal studies using invasive methods to assess tissue damage. This damage can take the form of vascular renal injury ranging from self-limited hematuria to perinephric/nephric hematomas. Numerous studies have described various complications including intraparenchymal, subcapsular and perirenal hemorrhage. There is evidence that even short-term exposure to shock waves can cause changes in the renal microvasculature. In addition, hemorrhage can trigger an inflammatory response that can lead to scarring with permanent loss of functional renal volume. In the long term, human and animal studies suggest that these acute hemorrhagic lesions may progress to scarring and complete atrophy of the renal papillae [2]. Complications were renal colic (grade 1) in 3 patients, hematuria (grade 1) in 1 patient, pyelonephritis (grade 2) in 1 patient and perirenal hematoma (grade 3a) in 1 patient in group 1. In group 2, renal colic (grade 1) in 2 patients, hematuria (grade 1) in 2 patients and urinary tract infection (grade 2) in 1 patient. There were no major complications. All complications were treated conservatively. According to the results of our study, there was no statistically significant difference in complications between the two groups.

Treatment protocols have been tried in many animal studies to minimize renal damage in ESWL treatment. Ramp and pause protocols have been observed to reduce damage. Many treatment protocols have been proposed to minimize renal injury. Stepwise voltage ESWL was effective in the treatment of urinary calculi in 31 children with acceptable success rates without morbidity [27]. In another study in humans, no statistically significant difference was found between treatment protocols [10]. The latest meta-analysis in the literature reported that escalating voltage ESWL offers comparable safety and efficacy to constant voltage ESWL [28]. In their prospective randomized study of 150 patients, Rabah et al. Compared constant, escalating and reduction energy ESWL protocols for renal stones. Although the stone-free rate was higher in the constant energy group, no statistically significant difference was found between the groups. In addition, no difference was found between the 3 groups in terms of complications [11]. Similarly, Skuginna et al. reported in their clinical study that a stepwise voltage ramping during ESWL was associated with a lower risk of renal damage compared with a constant maximal voltage without compromising treatment efficacy [12]. In a prospective randomized study of 40 patients, they found no statistically significant difference in stone fragmentation (75% vs. 72%, respectively) comparing stepwise and constant voltage strategy [13]. Skuginna et al. reached the same result in their study with 418 patients in two groups (stepwise and fixed) and reported this rate as 72.2% versus 74.5% [12]. Demirci et al. compared the results of the two treatment methods 8 weeks after the first treatment and found that the success rate in the stepwise ESWL group was statistically significantly higher than in the conventional group (stone free rate 96% (24/25) and 72% (18/25), p<0.05) [7]. In another study, Lambert et al. Compared stepwise and fixed protocol ESWL treatment in 45 patients and found a statistically significant difference in favour of the stepwise method in terms of both stone fragmentation and less renal tissue damage (81% versus 48%, p=0.03) [8]. In our study, we found no statistically significant difference between the two ESWL treatment protocols in terms of primary and secondary outcomes. In terms of stone free rate, we achieved a stone free rate comparable to other randomized trials and even higher.

Our study has some limitations. These include not comparing TIMP-2 and IGFPB7 levels with GFR and creatinine clearance, and not analyzing long-term outcomes. Another limiting factor is that early renal damage, especially renal perfusion, was not correlated with radiological examination in our study. Larger, prospective, case-controlled studies to further identify patients at risk of renal injury after ESWL may help to confirm our results.

Conclusion

In this prospective, randomized study, a significant increase in TIMP-2, IGFBP7 and combination levels was observed after ESWL treatment with two different protocols. This showed that these two biomarkers can be used to determine acute renal injury in patients undergoing ESWL. In contrast, a statistically significant effect of a stepwise voltage ramping on renal injury compared to a constant maximal voltage was not detected by evaluating urinary TIMP-2 and IGFBP7. Furthermore, no significant difference in treatment efficacy was observed between the two ESWL protocols. More detailed studies including long-term follow-up are needed to determine these early changes in renal physiology due to ESWL with shock waves and the long-term results.

Ethics Committee Approval: The study was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Health Application and Research Centre (Approval date, and registration number: 2016- 110).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – K.G.S., F.A.A.; Design – K.G.S., F.A.A.; Supervision – K.G.S., E.G., S.S., V.T.; Resources – A.K., R.T., M.G.Y., E.G.; Materials – A.K., R.T., M.G.Y., E.G.; Data Collection and/or Processing – A.K., R.T., M.G.Y., E.G.; Analysis and/or Interpretation – A.K., R.T., M.G.Y., E.G.; Literature Search – A.K., R.T., M.G.Y., E.G.; Writing Manuscript – K.G.S., F.A.A.; Critical Review – K.G.S., V.T., A.I.T.

Conflict of Interest: The authors declare that they have no conflicts of interest.
Financial Disclosure: Financial support was provided by Bakırköy Dr. Sadi Konuk Health Application and Research Centre Education Planning Board for the analysis of TIMP 2, IGFBP 7 and Beta-2 microglobulin levels.

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