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Renal protective effect of *N*-acetylcysteine with stepwise ramping voltage against extracorporeal shock wave lithotripsy-induced renal injury: a prospective randomized trial

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Abstract

Purpose To evaluate the role of combination of *N*-acetylcysteine with stepwise ramping voltage in renal protection against the ischemic, vascular and oxidative effects of extracorporeal shock wave lithotripsy.

Patients and methods A prospective randomized trial on 164 adult patients scheduled for ESWL for single renal stones. Patients with radio-lucent stones, diabetes, hypertension, febrile UTI, and preoperative albuminuria were excluded from the study. Patients were randomized into one of four groups. Group A patients received maximal fixed voltage of ESWL. Group B patients received stepwise ramping voltage of ESWL. Group C patients received fixed maximal voltage with *N*-acetylcysteine (NAC) 600 mg/bid from 48 h before to 24 h after the procedure. Group D patients received gradual ramping voltage with NAC. Urinary β_2-microglobulin, 24 h albumin and *N*-acetyl-β-D-glucosaminidase/creatinine ratio at 1 day and 5 days post-ESWL and the stone free rate at 2 weeks were measured.

Results Group D was the only group that showed no significant difference pre and post ESWL in urinary albumin, β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase/creatinine ratio. Post hoc analysis revealed no significant difference between group B and group C in albumin, β_2-microglobulin *N*-acetyl-β-D-glucosaminidase/creatinine ratio, but both of them had significantly lower levels than group A and significantly higher levels than group D. There was no statistically significant difference between all groups in the stone free rate at 2 weeks.

Conclusion *N*-acetylcysteine protects the kidney against ESWL-induced renal injuries especially if combined with stepwise ramping voltage.

Keywords ESWL · NAC · Ramping · Micro-albumin · β_2-microglobulin

Introduction

Urolithiasis is a common health problem worldwide. Its exact pathophysiological basis of formation is not yet clear, as there are different types of it and being too complex to be understood. Sometimes, it may lead to progressive renal morbidity. Therefore, in many cases, stone elimination should be done as soon as possible. The appropriate modality of treatment should be considered to provide the highest efficacy with the lowest morbidity [1, 2]. Throughout the last decades, extracorporeal shockwave lithotripsy (ESWL) has become one of the most commonly used urological procedures for urolithiasis. According to the European Association of Urology (EAU) guidelines, it is considered the first-line treatment for most renal stones of < 2 cm [3, 4]. Many structural and vascular complications were recorded especially with multiple sessions ESWL treatments and high energy shock waves. The main bad effects of ESWL on renal tissue include the vascular effect e.g. bleeding and hematoma (caused by physical force), the ischemic effect (caused by vasoconstriction), and the inflammatory reaction

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with the liberation of oxygen free radicals that may affect the renal function [5–8]. Renal glomerular and tubular cells damage results in appearance or increased urinary levels of certain substances e.g. albumin, β_2-microglobulin, and cellular enzymes such as *N*-acetyl-β-D-glucosaminidase (NAG), β-galactosidase, γ-glutamyl transaminase, heart fatty acid-binding protein, cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) [4, 9–11]. Urologists spend great effort aiming for improving ESWL results and minimizing the complications either by adding renal protective substances or modifying the technique of shockwave delivery to the kidney. Stepwise voltage ramping can significantly reduce the extent of renal parenchymal hemorrhagic lesions and may even provide a protective effect compared to fixed voltage treatment [12]. *N*-acetylcysteine (NAC) is a thiol-containing cell membrane permeable antioxidant that eliminates a large spectrum of reactive oxygen species (ROS). These ROS increase the tissue damage by enhancing lipid perioxidation, opposing the antioxidants and promoting DNA damage, leukocyte activation and cytokine production [13]. NAC also increases the level of glutathione, a potent vasodilator, preventing regional vasoconstriction. So, NAC has an important role in nephron-protection from ischemic and toxic acute renal failure [14, 15]. In this study, we evaluated the protective effect of NAC and stepwise voltage ramping for ESWL-induced renal injury.

Patients and methods

After local ethics committee approval number 3626 and informed consent from all patients was obtained, we conducted this prospective randomized trial between April 2017 and August 2019 on 164 adult patients scheduled for ESWL for single renal stone (< 2 cm). Patients with radio-lucent stones, diabetes, hypertension, uncontrolled coagulopathy, febrile urinary tract infection, age less than 18 years and preoperative albuminuria (> 300 mg/L) were excluded from the study. All patients were evaluated before the procedure with history, routine laboratory tests (urine analysis, serum creatinine, complete blood count, and coagulation profile), and estimation of urinary 24 h albumin using ARCHITECT c4000 system (Abbott Diagnostics, Santa Clara, CA, USA), urinary β_2-microglobulin using B2M Elisa kit (ASSAYPRO/USA), and urinary NAG and creatinine using a double-antibody sandwich enzyme Linked immunosorbent assay (ELISA) (Roche Diagnostics Ltd. Bell Lane, Lewes, Sussex. BN71LG). Eligible patients were randomized into one of four groups using closed envelopes. Group A patients received 2000–3000 shocks with a fixed voltage of 70 MPa and 0.7 mJ/mm^2 delivered at 80 shocks/min from the start. Group B patients received 2000-3000 shocks with stepwise voltage ramping from 49 MPa with 0.35 mJ/mm^2 and increased by one step for every 200 shocks up to step 4, which delivered 70 MPa and 0.7 mJ/mm^2. Group C patients received 2000–3000 shocks with fixed maximal voltage of 70 MPa and 0.7 mJ/mm^2 delivered at 80 shocks/min from the start with oral NAC 600 mg/bid prescribed from 48 h before to 24 h after the procedure. Group D patients received 2000–3000 shocks with gradual ramping voltage from 49 MPa with 0.35 mJ/mm^2 and increased by one step for every 200 shocks up to step 4, which delivered 70 MPa and 0.7 mJ/mm^2 with oral NAC 600 mg/bid prescribed from 48 h before to 24 h after the procedure. ESWL was performed using the Dornier lithotripter device S (Dornier MedTech GmbH, Germany) with the electromagnetic shockwave source. The patients received 1 mg/kg meperidine hydrochloride i.v. for analgesia with maximum dose 600 mg/24 h. All patients were followed up the day after ESWL (by urinary β_2-microglobulin, urinary 24 h albumin, urinary NAG/creatinine ratio and pelvi-abdominal ultrasound) to detect glomerular and tubular damage and detect any renal or peri-renal hematomas, 5 days after ESWL (by urinary β_2-microglobulin, urinary 24 h albumin and urinary NAG/creatinine ratio), 2 weeks after ESWL (by ultrasound and plain X-rays) to follow up the renal or peri-renal hematomas and detect the stone free rate.

Outcome measures

The primary outcome was the difference in albuminuria, β_2-microglobulinuria levels and urinary NAG/creatinine ratio between all groups. Secondary outcome was the assessment of stone free rate and presence/abscense of renal/peri-renal hematoma.

Statistical analysis

The sample size was calculated providing that the effect size is 0.5 with a error protection of 0.05 and 80% power of the study. After adding 10% for possible drop out or loss during follow-up, the sample size was at least 37 patients in each group. Data were collected, coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Data were tested for normal distribution using the Shapiro Walk test. According to the type of data, quantitative continuous data were represented by mean ± SD, while categorical data were represented by number (absolute frequency) and percentage (relative frequency). Differences among quantitative independent multiple groups were tested by one-way ANOVA when normally distributed and Kruskal–Wallis when the data were not normally distributed. While differences among qualitative independent multiple groups were tested by Chi square test. Paired analysis by paired *t* test was used for comparison

between pre-ESWL and post-ESWL results. Post hoc analysis using the Bonferroni test was done when there were significant differences between groups. *P* value was set at < 0.05 for significant results & < 0.001 for high significant results.

Results

Two hundred eighty-eight patients were tested for eligibility for the study inclusion criteria, 164 patients fulfilled inclusion and exclusion criteria and agreed to participate. They were allocated after randomization into four groups. The final analysis was performed for the patients who completed the study. The flow of patients in the study is shown in the Consolidated Standards of Reporting Trials (CONSORT) chart (Fig. 1). Patients' baseline characteristics and demographic data before ESWL were comparable between all groups (Table 1). By Comparing urinary levels of β_2-microglobulin, 24 h albumin and NAG/creatinine ratio in each group before and 1 day after ESWL, group D was the only group that showed no significant difference pre and post ESWL ($P = 0.091$, 0.084 & 0.062 respectively) (Table 2). There were statistically significant differences between all groups for the urinary levels of albumin, β_2-microglobulin and NAG/creatinine ratio at 1 day after ESWL ($P < 0.001$, $P < 0.001$ & $P < 0.001$ respectively). However, there were no statistically significant differences between all groups for the urinary levels of albumin, β_2-microglobulin and NAG/creatinine ratio after 5 days of ESWL ($P = 0.094$, $P = 0.074$ & $P = 0.065$ respectively) (Table 3). Post hoc analysis revealed that group A showed significantly higher levels of urinary albumin, β_2-microglobulin and NAG/creatinine ratio in comparison to other groups. While, group D showed significantly lower levels of albumin, β_2-microglobulin and NAG/creatinine ratio in comparison to other groups. No significant difference between group B and group C in albumin and β_2-microglobulin and NAG/creatinine ratio ($P = 0.793$, $P = 0.311$ & $P = 0.421$) respectively, but both of them had significantly lower levels than group A and significantly higher levels than group D (Supplementary Table 1). There was no statistically significant difference between all groups either in the stone free rate at 2 weeks or the formation of a renal or peri-renal hematoma ($P = 0.195$ and $P = 0.652$ respectively). There was temporary hydronephrosis of the ipsilateral pelvi-calyceal system in 39 patients at 1 week after ESWL due to the presence of stone fragments in the ureter with no significant difference between all groups ($P = 0.742$) (Table 3).

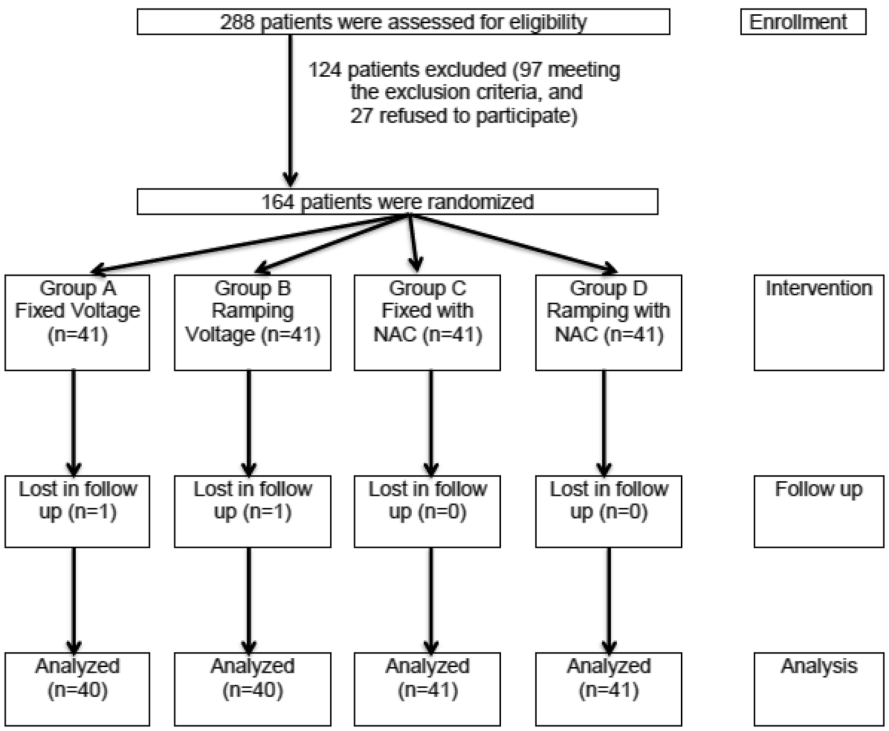

Fig. 1 Consolidated Standards of Reporting Trial (CONSORT) flow diagram of the patients through the study. NAC *N*-acetylcysteine

NAC: N-acetylcysteine

Table 1 Patient characteristics: comparison between different groups before intervention

	Group A Fixed voltage	Group B Ramping voltage	Group C Fixed voltage with NAC	Group D Ramping voltage with NAC	*P* value
Categorical data, *N* (%)					
Sex					
Male	24 (60)	27 (67.5)	27 (65.8)	25 (60.9)	0.395†
Female	16 (40)	13 (32.5)	14 (34.2)	16 (39.1)	
Side					
Right	21 (52.5)	23 (57.5)	21 (51.2)	27 (65.8)	0.691†
Left	19 (47.5)	17 (42.5)	20 (48.8)	14 (34.2)	
Continuous data, mean ± SD					
Age (years)	41.3 ± 9.8	37.5 ± 12.3	38.6 ± 10.4	39.5 ± 10.6	0.173‡
BMI (kg/m^2)	28.7 ± 2.36	27.7 ± 3.53	28.4 ± 4.32	29.1 ± 4.61	0.619‡
Stone density (HU)	754.73 ± 145.1	787.33 ± 141.4	765.73 ± 150.02	777.33 ± 140.44	0.123‡
Stone largest diameter (mm)	14.9 ± 2.54	13.7 ± 2.12	15.2 ± 2.56	14.7 ± 2.32	0.253‡
Urinary Albumin before (mg/24 h)	15.53 ± 3.16	14.13 ± 3.71	15.13 ± 3.66	15.33 ± 3.57	0.76‡
Urinary β_2 Globulin before (μg/mL)	0.121 ± 0.039	0.128 ± 0.041	0.127 ± 0.067	0.129 ± 0.072	0.187*
NAG/creatinine ratio (μmol/min/mmol creatinine)	0.22 ± 0.07	0.21 ± 0.08	0.24 ± 0.03	0.20 ± 0.07	0.27*
Number of shock-waves	2451 ± 177	2512 ± 172	2488 ± 181	2414 ± 184	0.98‡

NAC N-acetylcysteine, *NAG N*-acetyl-β-D-glucosaminidase, †Chi square test, ‡One-way ANOVA test, *Kruskal–Wallis test

Discussion

Inspite of its high popularity, low invasiveness and a success rate of 60–90% in renal stones < 2 cm, the safety of ESWL on the kidney is not completely guaranteed [3, 4]. Emergence of new generations of lithotripters increased the frequency of renal hematomas with its long-term effects due to smaller focal zones and higher peak pressures [16]. Many urinary markers could be used in monitoring ESWL-induced renal injury. In our study, we used albumin for detecting glomerular cell damage. To avoid the confounding effect of diuresis, we used the 24 h urinary albumin. While for assessing the tubular cell damage, we used urinary β_2-microglobulin and NAG/creatinine ratio. NAG is a urinary enzyme found in the lysosomes of epithelial cells of the renal proximal tubule. It has a high molecular weight, so it is found in urine only by secretion from proximal tubular cell lysosomes due to proximal tubular cell injury [11]. Many studies were performed aiming to the protection of the kidney from the possible hazardous effects of ESWL either by optimization of energy protocols or using anti-oxidant drugs without compromising clinical effectiveness [17–21]. The concept of using a stepwise voltage ramping ESWL becomes a quite certain protocol in improving stone fragmentation and also limiting renal injury [22, 23]. NAC is a thiol antioxidant. The benefit of NAC administration for the prevention of contrast-induced nephropathy in patients with renal impairment undergoing contrast-enhanced CT was first described by Tepel et al. [24]. After that, some studies have shown benefits like those reported previously in patients undergoing contrast after NAC supplementation [25]. Unfortunately, there is no consensus in the literature to formulate any evidence-based recommendation on the use of NAC for reducing contrast-induced nephropathy (CIN). However, Renfan et al. reviewed randomized trials evaluating the efficacy of NAC for lowering the risk of CIN [26]. In addition, Wen-Qi et al. in a meta-analysis reported that Statin with NAC and intravenous saline seems to be the most effective treatment for the prevention of CIN [27]. NAC has the potential to prevent CIN risk due to its potent antioxidant and vasodilating actions secondary to increased expression of nitric oxide synthase increasing nitric oxide production which has the effect of vasodilation and the attenuation of ischemic renal failure. In addition, NAC inhibits renal cell apoptosis in a dose-dependent manner. NAC could increase plasma levels of reduced glutathione, an oxygen free-radical scavenger, and could inhibit oxidative stress in the post-ischemic kidney [28]. Another renal protective effect of NAC was reported by Ceylan et al. against colistin induced nephrotoxicity which is a primary treatment for multidrug-resistant bacteria. This was achieved by activation of superoxide dismutase enzyme 2 (SOD2), endothelial nitric oxide synthase enzyme (eNOS), and matrix metalloproteinase enzyme 3 (MMP3) protein expressions [29]. In the current study, we tried to get benefit from this renal protective effect of NAC during ESWL. To our knowledge, it is the first time to use it for this purpose. We tried also to maximize renal protection by a combination of NAC administration and stepwise ramping voltage

Table 2 Change assessment in urinary albumin, β_2-microglobulin and NAG/creatinine ratio in each group

	Mean ± SD	Paired *t*	*P*
Urinary albumin (mg/24 h)			
Group A (fixed voltage)			
Baseline	15.53 ± 3.16	− 22.8	< 0.001**
1 day after	650.2 ± 78.99		
Group B (ramping voltage)			
Baseline	14.13 ± 3.71	− 16.2	< 0.001**
1 day after	529.1 ± 86.07		
Group C (fixed voltage with NAC)			
Baseline	15.13 ± 3.66	− 10.02	< 0.001**
1 day after	551.1 ± 85.09		
Group D (ramping voltage with NAC)			
Baseline	15.33 ± 3.57	− 2.75	0.091
1 day after	99.1 ± 16.07		
Urinary β_2-microglobulin (μg/mL)			
Group A (fixed voltage)			
Baseline	0.121 ± 0.039	− 453.49	< 0.001**
1 day after	0.741 ± 0.229		
Group B (ramping voltage)			
Baseline	0.128 ± 0.041	− 312.45	< 0.001**
1 day after	0.214 ± 0.067		
Group C (fixed voltage with NAC)			
Baseline	0.127 ± 0.067	− 231.21	< 0.001**
1 day after	0.217 ± 0.077		
Group D (ramping voltage with NAC)			
Baseline	0.129 ± 0.072	− 1.7	0.084
1 day after	0.131 ± 0.079		
NAG/creatinine ratio (μmol/min/mmol creatinine)			
Group A (fixed voltage)			
Baseline	0.22 ± 0.07	− 53.29	< 0.001**
1 day after	0.79 ± 0.21		
Group B (ramping voltage)			
Baseline	0.21 ± 0.08	− 49.35	< 0.001**
1 day after	0.52 ± 0.18		
Group C (fixed voltage with NAC)			
Baseline	0.24 ± 0.03	− 50.31	< 0.001**
1 day after	0.53 ± 0.17		
Group D (ramping voltage with NAC)			
Baseline	0.20 ± 0.07	− 3.7	0.062
1 day after	0.29 ± 0.06		

NAC N-acetylcysteine, *NAG N*-acetyl-β-D-glucosaminidase, **significant

in ESWL to achieve this synergistic effect to minimize vasoconstriction, renal ischemia and oxidative stress pattern by NAC and decrease renal parenchymal hemorrhage and vasoconstriction by the ramping voltage. In this study also, we did not find a significant difference in stone free rate between all groups either using maximal fixed voltage or stepwise ramping voltage. These results matched with other studies [23, 30]. While, other studies mentioned that ramping voltage ESWL gives better results of stone disintegration and stone free rates [12, 22]. In the current study, group D was the only group that showed no significant difference pre and post ESWL in urinary levels of albumin, β_2-microglobulin and NAG/creatinine ratio meaning that combination of NAC with stepwise ramping voltage had the maximal protecting effect against renal glomerular and tubular damage during ESWL. Post hoc analysis revealed no significant difference between group B and group C in albumin, β_2-microglobulin and NAG/creatinine ratio, but both of them had significantly

Table 3 ESWL outcomes: comparison between different groups after intervention

	Group A Fixed voltage	Group B Ramping voltage	Group C Fixed voltage with NAC	Group D Ramping voltage with NAC	*P* value
Categorical data, *N* (%)					
Stone free rate	35 (87.5)	36 (90)	34 (85.4)	35 (87.8)	0.195†
Hematoma	3 (7.5)	3 (7.5)	2 (4.8)	2 (4.8)	0.652†
Conservative	3 (7.5)	3 (7.5)	2 (4.8)	2 (4.8)	
Blood transfusion	0 (0)	0 (0)	0 (0)	0 (0)	
Intervention	0 (0)	0 (0)	0 (0)	0 (0)	
Fever	6 (15)	7 (17.5)	6 (14.6)	5 (12.2)	0.855†
Obstruction of treated renal unit	10 (25)	9 (22.5)	10 (24.3)	10 (24.3)	0.742†
Continuous data, mean ± SD					
Urinary Albumin 1 day after (mg/24 h)	650.2 ± 78.99	529.1 ± 86.07	551.1 ± 85.09	99.1 ± 16.07	< 0.001‡
Urinary Albumin 5 days after (mg/24 h)	65.57 ± 9.22	64.43 ± 8.79	62.53 ± 8.67	57.33 ± 8.51	0.094‡
Urinary β_2-microglobulin 1 day after (μg/mL)	0.741 ± 0.229	0.214 ± 0.067	0.217 ± 0.077	0.131 ± 0.079	< 0.001*
Urinary β_2-microglobulin 5 days after (μg/mL)	0.165 ± 0.089	0.158 ± 0.081	0.157 ± 0.069	0.130 ± 0.074	0.074*
NAG/creatinine ratio 1 day after (μmol/min/mmol creatinine)	0.79 ± 0.21	0.52 ± 0.18	0.53 ± 0.17	0.29 ± 0.06	< 0.001*
NAG/creatinine ratio 5 days after (μmol/min/mmol creatinine)	0.31 ± 0.09	0.29 ± 0.15	0.30 ± 0.17	0.29 ± 0.19	0.065*

NAC N-acetylcysteine, *NAG N*-acetyl-β-D-glucosaminidase, †Chi square test, ‡One-way ANOVA test, *Kruskal–Wallis test

lower levels than group A and significantly higher levels than group D. Many studies were conducted to protect the kidney during ESWL or against CIN by many agents both in animals and human models e.g. antioxidants (selenium, A, C, and E), angiotensin receptor blockers, calcium channel blocker, mannitol, carnitine, tadalafil or even sirolimus [4, 19–21, 31–34].

Limitations of the study include the relatively small number of patients which could be increased in future studies. Another limitation is that there is no consensus about the appropriate dose of *N*-acetylcysteine. Finally, more protection of the kidney may be achieved if NAC is combined with other anti-oxidant agents.

Conclusion

N-acetylcysteine decreases the hazardous effect of ESWL-induced renal injuries which was detected by significantly decreasing post-ESWL urinary albumin, β_2-microglobulin and NAG/creatinine ratio specially if combined with stepwise ramping voltage.

Compliance with ethical standards

Conflict of interest The authors declare that they have no relevant financial interests or conflict of interest.

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