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ORIGINAL ARTICLE

Impact of N-Acetyl Cysteine in Reducing Urinary β2-Microglobulin as Biomarker for Renal Injury Post ESWL in Pediatrics

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ABSTRACT

Background: β2-microglobulin levels in urine have been measured to determine the role of N-acetylcysteine in renal protection against the oxidative, vascular, and ischemic effects of extracorporeal shock wave lithotripsy.

Method: It is planned to conduct a prospective randomized trial on 56 pediatric patients under the age of 18 years with a renal pelvic single stone at extracorporeal shockwave lithotripsy (SWL). Patients with radiolucent stones, kidney stone larger than 20 mm in diameter, chronic kidney diseases (CKD), urological congenital anomalies, and patients who had coagulopathy problems were excluded from the study. Two groups of patients were randomly assigned. N-Acetyl cysteine (NAC) was given to group A for 3 days before and 3 days after SWL (100 mg three times daily for pediatrics till seven years and 200 mg three times daily to whom from seven to eighteen year). Group B received placebo. The levels of B2 microglobulin in both groups were measured 3 days before and after SWL.

Results: no significant difference was found in urinary β2-mi croglobulin level at pre swl in both groups. However, at post swl, urinary B2 microglobulin level in group (A) was significantly lower than group (B). Stone-free rates at 2 weeks did not differ statistically from one group to anot her.

Conclusions: As far as pediatrics is concerned, N-acetylcysteine may show promising results in preventing SWL-induced renal injury.

Key words: SWL; NAC; B2 -microglobulin; Pediatrics.

INTRODUCTION

In many parts of the world urolithiasis is a common condition. We don't know its exact pathophysiological basis because it comes in different forms, and it is too complex to understand. If left untreated, it can lead to a progressive kidney disease. Consequently, in many cases, stone removal should be done right away, if at all possible. The most effective treatment with the least amount of morbidity should be considered [1,2]. Extracorporeal shockwave lithotripsy (SWL) has become one of the most common urological procedures for urolithiasis management in recent years. If the patient has a kidney stone that is less than 2 cm in diameter, European Association of Urology (EAU) guidelines suggested that ESWL is considered the first-line treatment [3,4].

Children with uncomplicated upper urinary tract calculi less than or equal to 20 mm should be treated with SWL. SWL can cause minor complications such as perirenal hematoma, bruising and hematuria, despite the fact that 68 to 92 percent of children are stone free after SWL [5].

It was found that ESWL treatments with multiple sessions and high energy shock waves resulted in many vascular and structural complications. The vascular effect of SWL on renal tissue is one of the most significant risks like the inflammatory reaction with the release of oxygen free radicals which affects the renal function, effect of ischemia (caused by vasoconstriction) in addition to hemorrhage and hematomas caused by physical force [6,7].

High levels of some substances appear in urine like β-galactosidase, N-acetyl-β-d-glucosaminidase (NAG), heart fatty acid binding protein, neutrophil gelatinase-

associated lipocalin (NGAL), cystatin C, β2-microglobulin and albumin which contribute to tubular and glomerular cell damage in the kidneys [4,8,9]. Urinary β2-microglobulin has been demonstrated to be a sensitive marker of renal tubular injury. Its increased excretion after ESWL procedure represents the proximal tubule cell damage together with kidney dysfunction following the treatment. This protein has low molecular mass and is easily filtrated and nearly reabsorbed by 100% in proximal tubules under physiological conditions. Its reuptake process is very efficient, hence any disturbance in its reabsorption results in increased amount of β2-microglobulin in urine, representing subtle changes in renal tubular function [10].

Urologists hardly work to improve ESWL results by adding renal protective substances or modifying the technique of shockwave delivery to the kidney, as well as minimizing the occurrence of complications. A wide range of reactive oxygen species (ROS) is being neutralized by a powerful antioxidant, N-acetylcysteine (NAC). By increasing lipid peroxidation, promoting DNA damage, opposing antioxidants, leukocyte activation, and cytokine production, ROS increase tissue damage [11]. While increasing glutathione, NAC prevents vasoconstriction in the region by increasing glutathione levels. Acute ischemic and toxic renal failure can be prevented by using NAC [12, 13]. After SWL, we evaluated NAC's ability to protect pediatric patients' kidneys from damage in our research.

METHODS

Written informed consent was obtained from all participants. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

A prospective randomized trial was conducted on all pediatric patients≤18 years of age with a renal pelvic solitary stone scheduled for SWL between April 2020 and April 2021. In a closed-envelope technique, all patients were randomly divided into two group: N-Acetyl cysteine was given to group A three days before and three days after the ESWL (100 mg three times daily for pediatrics till seven years and 200 mg three times daily to whom from seven to eighteen year. Group B received placebo [14]. Each group was split up into three groups:

- From 1 to 4 years.
- From 5to 10 years
- From 11 to 18 years.

Patients with radiolucent stone, kidney stone larger than 20 mm in diameter, chronic kidney diseases (CKD), urological congenital anomalies and with hemostatic disorders were excluded from the trial. Before the procedure, all patients were evaluated with a thorough medical history and examination tests such as serum creatinine; complete blood count; coagulation profile; evaluation of urinary B2 microglobulin levels before SWL; urine culture and sensitivity; pelvi-abdominal ultrasonography; low dose non contrast spiral CT abdomen & pelvis.

Patients were positioned in the supine position under general anesthesia. SWL was performed by electromagnetic Dornier Lithotripter S (Dornier MedTech-Munich, Germany), energy 10 -14 kV for about 45 min according to the density of the stone. Assessment of b2 microglobulin 3 days post SWL in both groups. Two weeks after SWL, all patients underwent an ultrasound to check for renal or peri-renal hematomas and to determine the stone-free rate in all patients.

Assessment of outcomes

The main result was β2 microglobulin different levels in the urine between the two groups. An evaluation of stone-free rate and the presence or absence of a renal/peri-renal hematoma was a secondary outcome.

Statistical Analysis:

Microsoft Excel software was used to code, enter, and analyze data collected during the patient's History, basic clinical examination, laboratory investigations, and outcome measures. We analyzed the collected information, depending on the data type (qualitative or quantitative), by statistical package called SPSS (Statistical Package for the Social Sciences) version 20.0. The P value was set at 0.05 for significant results, and at > 0.001 for highly significant results. The following tests were used to test the significance of differences based on the type

of data. The Chi square test (X2) for differences and associations between qualitative variables and the t test to differentiate between quantitatively independent groups. An acceptable P-value was set at 0.001 for highly significant results.

RESULTS

Fifty-six patients were included in our study, seven patients lost follow-up, so forty-nine patients conducted our study, 24 patients in group (A) and 25 patients in group (B) (Fig. 1).

A comparison of the baseline characteristics and demographics of both groups of patients was made before SWL (Table 1). Stone characters distribution and stone density between the studied groups is shown in (Table 2). The number of Extracorporeal shock wave lithotripsy (SWL) sessions and number of shockwaves distribution between studied groups is presented in (Table 3). There was no significant difference found in pre ESWL β2microglobulin level between the two groups. Post ESWL, β2microglobulin level in both groups was significantly increased and was significantly lower in group (A) than group (B). The highest level of β2microglobulin in urine post SWL was in patients from one to four years in group B (table 4). Stone-free rate and the formation of a renal or peri renal hematoma did not differ significantly between groups in post SWL follow up for 2 weeks by ultrasound and low dose non contrast CT (table 5).

Table 1: Demographic Data

			Group A	Group B		
			Group with N-acetylcysteine (N=24)	Group without N-acetylcysteine (N=25)	t/ X^2	P
Age			9.3±3.32 year	9.0±2.81 year	0.032	0.998
Sex	Girls	N	10	12		
		%	41.7%	48.0%		
	Boys	N	14	13	0.19	0.65
		%	58.3%	52.0%		
Total		N	24	25		
		%	100.0%	100.0%		

Mean age was 9.3±3.32 year and 9.0±2.81year in group (A) and group (B) respectively with no significant difference between them. There was no significant difference in sex distribution between groups.

Table 2: Stones characters distribution between studied group

			Group A	Group B		
			Group with N-acetylcysteine (N=24)	Group without N-acetylcysteine (N=25)	t/ X^2	P
Greatest dimension /CM			1.63±0.39	1.31±0.41	1.389	0.218
Size /CM^2			1.81±0.60	1.65±0.45	1.244	0.258
Density			828.20±96.02	841.12±97.49	-0.467	0.643
Site	Left	N	10	12		
		%	41.7%	48.0%		
	Right	N	14	13	0.19	0.65
		%	58.3%	52.0%		
Total		N	24	25		
		%	100.0%	100.0%		

The greatest dimensions were 1.63±0.39 and 1.31±0.41 respectively with no significant difference between groups. Stone size was 181.37±60.6 and 165.28±45.94 without significant difference between the two groups. There was no significant difference in density and the side of stone between groups.

Table 3: Number of extracorporeal shock wave lithotripsy ESWL sessions distribution between studied groups

			Group A	Group B	X^2	P
			Group with N-acetylcysteine	Group without N-acetylcysteine		
Shockwave mean± SD			1930.36±250	1895.2±310.6	1.483	0.185
Sessions	One	N	22	22		
		%	91.5%	88.0%		
	Two	N	2	3	0.38	0.81*
		%	8.5%	12.0%		
Total		N	24	25		
		%	100.0%	100.0%		

There was no significant difference between groups.

Table 4: β2-microglobuline distribution pre and post ESWL.

Age		Group	Mean	Std. Deviation	t	P
1-4 year	Pre_B2micro_globuline	Group (A)	56.4000	4.09878	1.098	0.309
		Group (B)	60.0000	5.77350		
	Post_B2micro_globuline	Group (A)	173.0000	16.04681	22.150	0.00**
		Group (B)	616.0000	41.60128		
5-10 year	Pre_B2micro_globuline	Group (A)	70.7143	22.24489	1.942	0.054
		Group (B)	59.1875	20.73714		
	Post_B2micro_globuline	Group (A)	213.2143	62.31456	5.679	0.00**
		Group (B)	332.5000	52.76868		
11-18 year	Pre_B2micro_globuline	Group (A)	116.0000	19.51922	1.301	0.229
		Group (B)	94.4000	31.57214		
	Post_B2micro_globuline	Group (A)	262.0000	40.09364	2.134	0.034*
		Group (B)	346.4000	109.18901		

Table 5: Stone free rate and renal hematoma distribution between studied groups.

			Group A	Group B	X^2	P
			Group with N-acetylcysteine	Group without N-acetylcysteine		
Stone free		N	21	23	0.27	0.603
		%	87.5%	92.0%		
Hematoma	-VE	N	22	24	0.4	0.52
		%	91.7%	96.0%		
	+VE	N	2	1		
		%	8.3%	4.0%		
Total		N	24	25		
		%	100.0%	100.0%		

No significant founded between groups

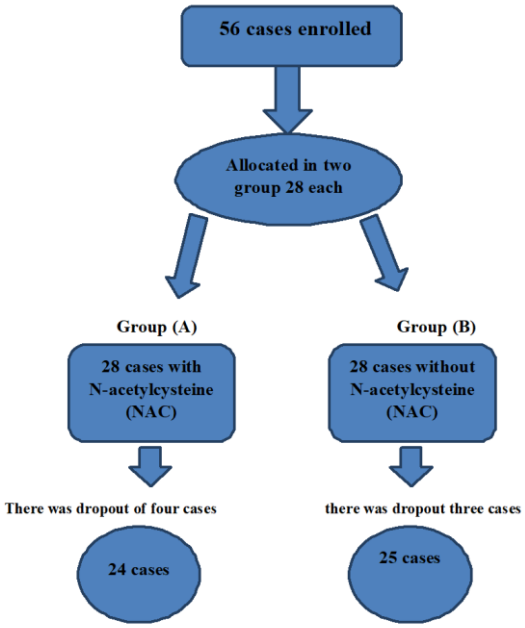

Figure 1. Consolidated Standards of Reporting Trial (CONSORT) flow diagram of the patients through the study

DISCUSSION

Most renal stones 2 cm in size are treated with extracorporeal shock wave lithotripsy (SWL) because of its high success rates, minimal invasiveness, and long-term safety with a lower trend of complications occurrence [15].

Shock waves cause traumatic vascular injury, which leads to blood vessel rupture and blood pooling in the renal parenchyma, according to previous studies. Urinary β2-microglobulin has been demonstrated to be a sensitive marker of renal tubular injury and its increased excretion after ESWL procedure represents the proximal tubule cell damage together with kidney dysfunction following the treatment. This protein has low molecular mass and is easily filtrated and reabsorbed nearly by 100% in proximal tubules under physiological conditions. β2-microglobulin reuptake process is very efficient, hence any disturbance in its reabsorption results in increased its amount in urine, representing subtle changes in renal tubular function [10].

In order to monitor ESWL-induced renal injury, a variety of urinary markers could be used. Numerous studies have been conducted in order to protect the kidney from the possible harmful effects of SWL by using antioxidant drugs [16,17]. When contrast-enhanced CT is performed on renally impaired patients, the benefit of NAC administration in preventing contrast-induced nephropathy (CIN) was first described by Tepel et al. [18]. Wen-Qi and co-authors, [19] reported that there is some evidence that statins combined with NAC and intravenous sodium chloride appear to be the most effective treatment for preventing CIN.

Xu et al. [20] reported that NAC supplementation was significantly and inversely associated with an increased risk of coronary artery disease in patients undergoing coronary angiography and computed tomography. In our study SWL in pediatrics, N acetylcysteine (NAC) has been used for the first time for this purpose, and we wanted to take advantage of its renal protective effect.

In our study, there was no significant difference found in pre SWL urinary β2-microglobulin level. However, post-SWL urinary β2-microglobulin in Group (A) was significantly lower than in group (B) and it was significantly increased in both groups. This is in agreement with Desoky et al. [21] who reported that β2-microglobulin was highly increased post ESWL in group without NAC and in agreement with Al-Awadi et al. [22] who reported that urinary albumin levels were significantly reduced post ESWL when oral antioxidants were given. In contrast, the study of El-Nahas et al. [4] reported that there were non-significant lower levels of urinary albumin when oral antioxidants were given. It may be according to the difference in the number of sessions between studies as in our

study the number of sessions was 1-2 sessions, while El-Nahas et al. reported the number of sessions was 1-4.

In our study, patients from one to four years in group B showed the highest level of urinary β2-microglobulin post ESWL. ESWL-induced renal damage and CIN have been studied extensively in both human and animal models. ESWL-induced renal damage and CIN have been studied extensively in both animal and human models, including antioxidants selenium (A, C, and E), mannitol, calcium channel blockers, tadalafil, carnitine, and even sirolimus [4, 22-24].

The current study was limited by a small number of patients, which could be increased in future studies. Also, there is no consensus on how much N-acetylcysteine is needed. As a final note, combining NAC with other antioxidant agents may enhance kidney protection.

CONCLUSION

Measuring urinary β2-microglobulin levels before and after extracorporeal shockwave lithotripsy N acetylcysteine showed promising results in protecting against SWL-induced renal injury.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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