

Assessment of Sympathetic Activity of Adrenal Medullae in Patients with Kidney Stone Treated by Extracorporeal Shock Wave Lithotripsy (ESWL)

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Abstract

Background: Extracorporeal shock wave lithotripsy (ESWL) is the most widely used method for treating kidney and upper ureteric stones smaller than 2 cm due to its effectiveness, safety, non-invasive, and an outpatient procedure. **Objective:** The present study aims to assess the effect of ESWL on the sympathetic activity of adrenal medullae in patients with renal stone. **Materials and Methods:** A cross-sectional study was conducted at the ESWL Unit, AL-Hilla Teaching Hospital, Babil Province, Iraq on 50 patients from October 1, 2021 to April 30, 2022. Before and right after an ESWL session, patients underwent a history, physical examination and laboratory tests to measure their levels of serum catecholamines (CAs). **Results:** The results of this study revealed that there is a significant increase of serum epinephrine and norepinephrine levels (P -value < 0.001) after ESWL session. There is a significant ($P < 0.1$) increase in epinephrine and norepinephrine levels in patients treated for upper pole renal stones when compared with mid and lower pole renal stones after having an ESWL session. Changing the lithotripter's parameters (energy, frequency, and number of shock waves) did not significantly ($P > 0.05$) correlate with the level of both norepinephrine and epinephrine in the serum after the ESWL session. **Conclusion:** The study found that patients with renal stones treated with ESWL had elevated serum CA levels after the session. The CA level correlates with the site of stone (the stone comes near to the adrenal medullae as there was an increase in the CA level), whereas it was unaffected by the lithotripter's parameters.

Keywords: Adrenal medullae, extracorporeal shock wave lithotripsy (ESWL), renal stone

INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is the only fully, non-invasive, outpatient method for the treatment of urinary tract stones. The effectiveness of ESWL is predicated on its capacity to pulverize calculi *in vivo* into smaller segments, which the body then expels spontaneously.^[1] Over 30 years, the lithotripters, which provide the energy required for this treatment, have gone through a number of advancements and adjustments; the electrohydraulic (HM-1) lithotripter was first described in 1980 and shortly followed by the electrohydraulic Dornier HM-3 lithotripter. Currently, advances in lithotripter models allow for shock wave generation from piezoelectric and electromagnetic properties.^[2] Second- and third-generation lithotripters have also utilized more narrow focal zones and higher peak pressures when compared

with the wider focal zones and lower pressures utilized by first-generation lithotripters.^[3] The selection between shockwave lithotripsy (SWL) and alternative treatment modalities is based on various factors,^[4] including the size of the stone, its burden, and its composition. ESWL is regarded a reasonable first-line treatment for non-staghorn renal and ureteral calculi that are smaller than 2 cm in size. Uric acid stones are more efficiently fragmented by SWL rather than calcium oxalate monohydrate, cysteine,

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and calcium phosphate stones.^[5] Despite the fact that it is non-invasive and safe modality, it has certain adverse implications; these adverse effects can be attributed to obstructive complications associated with stone passage, direct tissue damage, or both. Studies have shown that ESWL has a direct effect on nearby tissues as adrenal glands.^[6]

MATERIALS AND METHODS

Study design and subjects

A prospective cross-sectional study was conducted on 50 patients (29 males and 21 females). Their age extended from 16 to 72 years, attending the ESWL Unit due to ESWL arranged for the first time. The referrals of patients were mainly from urologists. The study was performed at the ESWL Unit, AL-Hilla Teaching Hospital, Babil Province, Iraq. The study was under supervision of Urosurgery and Medical Physiology Departments/College of Medicine/University of Babylon, Iraq, from October 1, 2021 to April 30, 2022.

Inclusion criteria

All patients included in the study are diagnosed to have renal stones 0.8–2 cm confirmed by imaging modalities and undergo an ESWL session for the first time.

Exclusion criteria

Patients who underwent ESWL session before, individuals with urinary tract stones other than kidney stones, and patients with adrenal gland disease were excluded.

History and clinical examination

A detailed history was taken from each patient regarding demographic data, daily life style, past medical history, past surgical history focusing on surgery related to urinary system, history of medication, and family history of renal stone. History of presenting illness focusses on symptoms related to urinary symptoms. General examination and vital signs of patients had been taken immediately before and after ESWL session and measurement of body mass index (BMI). Patients underwent biochemical testing, and a sample of blood was taken from each patient 5 min before and immediately after undergoing ESWL treatment (within less than 10 min) and sent for laboratories for the measurement of serum catecholamine (CA) level.

Patient preparation for ESWL

Patients were advised to stop eating or drinking 2–4 h before the procedure and to stop smoking if they smoked and caffeine-containing foods and beverages such as coffee, tea, or cola must be avoided before the procedure. Drugs such as aspirin-containing medications, anticoagulants, platelet inhibitors, and non-steroidal anti-inflammatory medicines should be discontinued 7–10 days before the session. Initial imaging documents confirm the presence

of stone (no., site, size, radiopacity of stone) and also detect if there is any urinary tract obstruction. In women of childbearing age, a pregnancy test is administered before session as there is risk of radiation exposure. In order to reduce pain during treatment and possibly increase success rates, patients receiving shock wave therapy for renal stones are uniformly given analgesia, often 30–60 min before the session. Patients ought to be informed of any potential consequences and failure risks. Then, in a specialized treatment room, which has the shock wave machine and imaging equipment, position is dictated by the location of the stone. The supine position of patients was used in this study for accurate localization of renal stone.

The procedure of treatment with ESWL

By using a Modulith SLX-F2 lithotripter (electromagnetic), a procedure takes about 0.5–1 h and sometimes longer depending on the size and number of the stones. First is stone localization: the stones to be treated are moved to the treatment focus using the localization system. An X-ray and/or a supplied ultrasound system can be used for this, by movement of the table until the stone lies within the focal point. Setting shock waves parameter (energy, frequency, and number of shock waves) and adjustment of ESWL parameter usually depend on the size, composition of the stone, as well as appearance of the stone as treatment progresses. ESWL is performed on an outpatient basis without the need for hospital admission following the procedure. At the time of discharge, patients are given a prescription for analgesics and a strainer to collect stone fragments during voiding for later analysis. After the procedure, patients are instructed to watch for signs of infection or obstruction as stone fragments are passed. After a few days, mild hematuria and flank soreness can be expected, and the patient ought to be informed of that previously, but persistent, heavy, gross hematuria or severe pain should prompt a re-evaluation and an assessment for bleeding complications.

Data analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (means $\pm$ SD). Student's *t*-test was used to compare means between the two groups. Paired *t*-test was used to compare means for two paired readings. Analysis of variance test was used to compare means between the three groups or more. Pearson's correlation coefficient (*r*) was used to find the relationship between two continuous variables. A *P*-value of ≤ 0.05 was considered significant.^[7]

Ethical consideration

All cases involved in this study were informed, and the consent was obtained verbally from each of them before

the samples were collected. The study was approved by the Committee of Publication Ethics at College of Medicine, University of Babylon, Babylon, Iraq, according to the document number 7266 on 8/9/2021.

RESULTS

The majority of patients ($n = 16$, 32.0%) were in the age group 30–40; more than half of the patients were males ($n = 29$, 58.0%) as shown in Table 1. Obese patients were present ($n = 19$, 38.0%) and the mean age of the patients was 44.40 ± 13.56 , with maximum age of 72.00 years and minimum age of 16.00 years. Mean BMI of patients was 29.05 ± 4.48 kg/m², with maximum BMI of 43.30 kg/m² and minimum BMI of 20.80 kg/m².

Distribution of patients according to clinical examination (blood pressure and pulse rate)

There were significant differences between means of systolic and diastolic blood pressures (mmHg) and pulse rate (bpm) pre- and post-ESWL, as shown in Table 2.

Table 1: Distribution of patients according to sociodemographic characteristics ($n = 50$)

Sociodemographic characteristics	Number	%
Age (years)		
< 30	4	8.0
30–40	16	32.0
40–50	12	24.0
50–60	10	20.0
60–70	6	12.0
≥ 70	2	4.0
Total	50	100.0
Gender		
Male	29	58.0
Female	21	42.0
Total	50	100.0
Body mass index (kg/m ²)		
Normal (18.5–24.9)	8	16.0
Overweight (25–29.9)	23	46.0
Obese (≥ 30)	19	38.0
Total	50	100.0

Table 2: The distribution of patients according to vital signs

Study variables	Periods of assessment	Mean $\pm$ SD	P-value
Systolic blood pressure (mmHg)	Pre-ESWL	126.60 $\pm$ 18.14	<0.001*
	Post-ESWL	142.40 $\pm$ 16.23	
Diastolic blood pressure (mmHg)	Pre-ESWL	76.20 $\pm$ 9.45	<0.001*
	Post-ESWL	80.50 $\pm$ 7.71	
Pulse rate (per min)	Pre-ESWL	90.06 $\pm$ 10.09	<0.001*
	Post-ESWL	98.88 $\pm$ 12.84	

Distribution of patients according to serum catecholamine level

The statistical analysis showed a significant increase of serum CA levels (epinephrine and norepinephrine) after undergoing ESWL session.

Correlation between mean differences of post-ESWL serum catecholamines level (pg/mL) and site of renal stone

The correlation between serum (epinephrine and norepinephrine) level following ESWL and the site of renal stone among patients of our study was found to be significant as there are considerable differences in the level of serum CAs across different sites of renal stone ($P = 0.05$), as displayed in Table 3.

Correlation between serum catecholamines level and energy of lithotripter

Assessment of the correlation of the mean differences of post-ESWL serum CAs level according to the energy (kV) of lithotripter including 2 and 2.5, 3 and 3.5, 4 and 4.5, and 5, 6 and 7 is shown in Table 4. There were no significant differences ($P > 0.05$) between means of epinephrine and norepinephrine (pg/mL) post-ESWL, according to power (energy in kV).

Correlation between serum catecholamine level and the frequency of lithotripter

The study attempted to demonstrate how changes of frequency can affect the level of CAs post-ESWL, as displayed in Table 5; there are no significant differences between means of CAs (pg/mL) post-session according to frequency.

DISCUSSION

The mean age of participants diagnosed with renal stones was 44.40 ± 13.56 years; the prevalence of renal stones reported in this study was the highest in the age group 30–40 (32%), which agreed with the previous study^[8] that was conducted in 14 countries, including Iraq, where the average age was 48 ± 14 years. The highest frequency of developing renal stones was when the patient was at the peak of his/her career; this confirms the hypothesis that dietary habits, metabolic rate, and lifestyle could be risk factors for renal stones. In contrast,^[9] a study conducted in the USA revealed that the overall prevalence of urinary stones appears to rise linearly with age, peaking between 60 and 70 years, whereas a German study^[10] found that individuals in their 40–49s who were middle-aged had a propensity toward an increasing incidence of renal stones. Regarding gender, 58% of the participants in this study was male, with a male–female ratio of 1:38, which resembles to the study^[11] with a male–female ratio of 1:57, as the concentration of urinary citrates is lowered in men owing

Table 3: The mean differences of catecholamine level pre- and post-ESWL according to the site of stone

Study variables	Site of stone	N	Mean $\pm$ SD	P-value
Epinephrine post-ESWL (pg/mL)	Lower pole	30	8.281 $\pm$ 5.277	<0.05
	Mid pole	9	7.739 $\pm$ 3.631	
	Upper pole	11	14.047 $\pm$ 5.206	
Norepinephrine post-ESWL (pg/mL)	Lower pole	30	179.899 $\pm$ 50.018	<0.05
	Mid pole	9	190.334 $\pm$ 48.269	
	Upper pole	11	195.275 $\pm$ 46.240	

Table 4: Correlation between the energy in kV and catecholamine level

Study variables	Energy (kV)	N	Mean $\pm$ SD	P-value
Epinephrine post-ESWL (pg/mL)	2 and 2.5	4	11.920 $\pm$ 3.924	0.537
	3 and 3.5	10	9.379 $\pm$ 6.981	
	4 and 4.5	11	7.589 $\pm$ 4.997	
	5 and 6	25	9.905 $\pm$ 5.328	
Norepinephrine post-ESWL (pg/mL)	2 and 2.5	4	165.669 $\pm$ 34.545	0.539
	3 and 3.5	10	171.925 $\pm$ 49.149	
	4 and 4.5	11	192.995 $\pm$ 62.067	
	5 and 6	25	192.645 $\pm$ 44.098	

Table 5: Correlation between the frequency of lithotripter and catecholamine level

Study variables	Frequency (Hz)	N	Mean $\pm$ SD	P-value
Epinephrine post-ESWL (pg/mL)	1.5	42	8.946 $\pm$ 5.404	0.138
	2 and 3	8	12.107 $\pm$ 5.597	
Norepinephrine post-ESWL (pg/mL)	1.5	42	187.871 $\pm$ 49.297	0.634
	2 and 3	8	178.804 $\pm$ 47.200	

to higher levels of phosphorus and magnesium in urine than in women. This is because males tend to consume more protein in their diets than females, which increases the risk of renal stone formation.^[12,13] Contrarily, estrogen in women causes them to produce a copious amount of citric acid, which decreases the risk of kidney stones formation. The mean BMI of patients in this study was 29.05 ± 4.48 . A previous study which was conducted in Saudi Arabia^[14] concluded that an increase in BMI plays a major role in the development of urinary stones. An increased risk of renal stone formation in overweight people may be related to those patients' poor dietary habits as well as bad lifestyle behaviors; higher BMI promotes urinary excretion of calcium, uric acid, and oxalate, thereby participating in stone formation. Type 2 diabetes mellitus and metabolic syndrome are more common in obese persons, so that they are more vulnerable to develop renal stones.^[15,16]

In this study, as displayed in Table 2, there are significant differences in the readings of systolic and diastolic blood pressures and pulse rate of patients who had ESWL session. Regarding blood pressure, as there is a significant increase in the plasma CA level of patients after ESWL session, this increase in readings of diastolic and systolic blood pressures as CAs plays a central role in the regulation

of blood pressure. Epinephrine and norepinephrine play a crucial role in controlling blood pressure, by contracting the smooth muscle in the vasculature (via alpha-1 receptors), and enhanced contractility of cardiac muscle (via beta-1 receptors) led to increased blood pressure.^[17] This agrees with the previous study,^[18] which showed that there is a risk of blood pressure rising in patients who have ESWL sessions. In contrast,^[19] the study showed that, immediately after ESWL session, systolic blood pressure significantly increases as opposed to diastolic blood pressure, which does not change. Our findings disagree with^[20] the study, which was carried out in the Iraqi city and revealed that patients who attended an ESWL session did not show any significant increase in blood pressure. Regarding pulse rate, as shown in Table 2 there were significant changes in the pulse rate after session. The most possible explanation for that is the elevation level of serum CA (as discussed subsequently), as activation of the sympathetic nervous system results in both positive (inotropic and dromotropic) effects. Similar to our study,^[21] their study revealed that there is a significant effect of undergoing ESWL and cardiac heart rate, and they hypothesized that either there is direct mechanical stimulation of the myocardium or a neurohumoral response to treatment or both. As shown in Table 6 from the current study, there were considerable

Table 6: The mean differences of catecholamines (pg/mL) between two periods of assessment (pre- and post-ESWL)

Study variables	Periods of assessment	Mean $\pm$ SD	P-value
Epinephrine (pg/mL)	Pre-ESWL	3.945 $\pm$ 2.758	<0.001*
	Post-ESWL	9.452 $\pm$ 5.503	
Norepinephrine (pg/mL)	Pre-ESWL	73.945 $\pm$ 2.758	<0.001*
	Post-ESWL	176.420 $\pm$ 48.610	

differences in the serum epinephrine and norepinephrine concentration of patients who underwent ESWL session. The most potential explanations for increasing serum CAs are direct effects of shock waves on the tissue surrounding the kidneys, the adrenal medullae, that lead to increased activity of sympathetic stimulation and the activation of chromaffin cells that secrete CAs into blood stream (epinephrine and norepinephrine).

Because of the fact that The catecholamines that secreted from adrenal medullae can persist in serum for minutes, contrary to those released direct from sympathetic nervous system, which does not enter the blood stream.^[22] The fight-or-flight response is one of the additional causes of increased catecholamines during ESWL, as having an ESWL session for the first time may be regarded as a stressful situation.^[23] Another potential cause of increased CA secretion from the adrenal medullae is the influence of cortisol, which is released from the adrenal cortex during stressful conditions and plays a crucial role in stimulating the adrenal medullae.^[24] Furthermore, a study^[25] earlier than 30 years ago indicated no noticeable elevation in CA levels in patients who were given ESWL sessions, which is in contrast to the findings of our study. Their study^[26] demonstrated a significant rise in epinephrine levels in patients receiving ESWL, which is in line with the results of the present study. Unfortunately, there is limited recent study about CA level in patients treated by ESWL.

Also, the study reveals that there was no significant correlation between CA level and lithotripter parameters (energy and frequency).

This may be due to the small sample size of the current study, which may have made the results inconclusive, or it may have been because different patients underwent parameter changes.

In contrast, the study stated that there was a significant correlation between stone site [Table 3] and level of serum CA, as there was more increase in level of epinephrine and norepinephrine in patients treated with upper pole renal stones, rather than those with lower and mid pole renal stones. A possible explanation for those changes relates to the location of the adrenal medullae. It is located closely above the kidneys; as additional excitement increased, it approached shock wave streams. Sympathetic activity increased, resulting in an increase in the releasing of CA. The other explanation could be sample-related; future

research with a larger sampling size would undoubtedly produce accurate results. Also, there has been limited research on the correlation between shock wave stream distance and adrenal medullae sympathetic activity.

CONCLUSION

The study found that participating in ESWL sessions increased the CA levels, and the most significant factor influencing the amount of serum CA level is the distance between the shock wave stream and the adrenal tissue as the stream gets closer as serum CA levels rise. There is no correlation between lithotripter parameter and the level of serum CA in patients who underwent ESWL for the treatment of renal stone.

Limitation of study

The limitation of the study was that it was done in a single center with single type of lithotripter.

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Conflicts of interest

There are no conflicts of interest.

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