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Urinary NAG excretion after anesthesia-free extracorporeal lithotripsy of renal stones: a marker of early tubular damage

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Summary. Second generation lithotripters require a higher number of shocks per session as well as an increased rate of secondary treatments for complete stone disintegration compared to the original spark gap lithotripter. The clinical relevance of biological side effects caused by such treatment are less known. We evaluated urinary excretion of N-acetyl-glucosaminidase (NAG) before and after lithotripsy in 50 patients treated with a low pressure spark gap lithotripter (Dornier HM3) and in 36 patients treated with a piezoelectric lithotripter (Wolf Piezolith 2200) in an attempt to evaluate their side effects on renal tissue. The urinary excretion of NAG increased after both spark gap lithotripsy using the modified HM3 and piezoelectric lithotripsy. These changes may be associated with slight tubular damage that would occur after anesthesia-free lithotripsy in patients subjected both to a high number of shocks and to secondary treatments.

Key words: Urinary enzyme – N-acetyl-glucosaminidase – Renal tubular damage – Extracorporeal shock wave lithotripsy (ESWL) – Anesthesia-free – Spark gap – Piezoelectric – Renal stone

The use of extracorporeal shock wave lithotripsy (ESWL) for renal stone treatment has been reported to be safe and effective.

Early reports ruled ut significant biological effects of the transmission of shock waves through the body, but in the developmental phase only a few shock waves were applied compared to clinical practice [1].

Successive animal studies revealed histological changes in the cortex and medulla of treated kidneys, the most significant of which were cortical linear and focal hemorrhages. Fibroblastic scars were observed at the sites of parenchymal bleeding in animal sacrificed after 3–6 months [5].

In clinical use intrarenal and perirenal abnormalities were reported in about 50% of the kidneys examined by CT or MRI following ESWL [4, 10]. Neither increases of serum creatinine or a decrease in creatinine clearance nor changes in renal function using scintigraphy were caused by ESWL, because the unaffected part of the renal parenchyma compensated for the part damaged [2, 6].

As demonstrated by histopathological and imaging studies renal damage is limited to the focused area, therefore it can be early diagnosed only by changes of very sensitive indicators such as excretion of urinary enzymes [7, 11]. Particularly urinary excretion of N-acetyl-glucosaminidase (NAG) is a very reliable marker of acute renal tubular damage [9].

In fact a slight increase of urinary NAG excretion was observed after ESWL by the first generation machines mainly in case of more than 2,000 shocks [12].

Low pressure spark gap lithotripsy and piezoelectric lithotripsy do not require anesthesia in the majority of the cases. The reduction of pain depends on the lower total energy and on the larger area of shock wave entry at the skin.

Different types of lithotripters produce different therapeutic and side effects; the use of new lithotripters might produce a lower risk of renal damage.

The present investigation was carried out to study the effect of anesthesia-free lithotripsy on renal tubular cells by measuring the urinary NAG before and after treatment.

Materials and methods

A total of 86 patients with renal stones were considered for lithotripsy. Stones with associated hydronephrosis or delayed function on the IVP were excluded.

Treatment by a modified Dornier HM3 lithotripter with a low pressure generator and a larger hemiellipsoid was compared with treatment by a Wolf Piezolith 2200 lithotripter.

Respectively 50 patients (26 women and 24 men) were treated with the modified Dornier HM3 lithotripter and 36 patients (19 women and 17 men) were treated with the piezoelectric Wolf lithotripter.

Mean patient ages were respectively 48.6 ± 11.8 (26–74) and 47.2 ± 15.3 (20–75). Patients treated by the modified Dornier received

Table 1. Serum and urinary enzymes before and after ESWL by low pressure spark gap lithotripter (Dornier HM3 modified)

	Total		> 2,600 Shocks (4 patients)		< 2,600 Shocks (26 patients)	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
GOT (U/l)	18 ± 6	18 ± 5	16 ± 4	16 ± 5	21 ± 8	20 ± 4
GPT (U/l)	20 ± 11	19 ± 8	16 ± 7	15 ± 3	25 ± 14	24 ± 10
Amylase (U/l)	139 ± 54	139 ± 53	149 ± 61	131 ± 48	125 ± 44	150 ± 59
LDH (U/l)	280 ± 84	336 ± 98**	277 ± 97	309 ± 90	290 ± 23	425 ± 77***
CK (U/l)	73 ± 26	171 ± 181***	67 ± 26	107 ± 98*	79 ± 26	236 ± 222***
NAG/CR (U/g)	7.41 + 6.87	12.77 + 12.38**	7.75 + 7.1	10.23 + 6.8	7.44 ± 6.6	15.83 + 15.3*

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2. Serum and urinary enzymes before and after piezoelectric extracorporeal lithotripsy (Wolf Piezolith 2200)

	Total		< 7000		> 7000	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
GOT (U/l)	22 ± 5	23 ± 8	21 ± 3	21 ± 0	22 ± 5	22 ± 10
GPT (U/l)	23 ± 20	20 ± 12	23 ± 9	22 ± 6	17 ± 8	17 ± 9
Amylase (U/l)	111 ± 58	107 ± 48	112 ± 44	136 ± 74	97 ± 37	95 ± 35
LDH (U/l)	267 ± 38	283 ± 49	226 ± 48	260 ± 39	276 ± 42	304 ± 59
CK (U/l)	71 ± 72	124 ± 65*	64 ± 33	81 ± 18	74 ± 100	154 ± 227
NAG/CR (U/g)	6.97 ± 5.26	9.99 ± 7.99*	6.83 ± 4.8	9.33 ± 0.8	8.81 ± 6.4	13.6 ± 7.4

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. Urinary NAG excretion after subsequent ESWL

	Preoperative	1st Treatment	2nd–3rd Treatment
Dornier HM3 Mod.	5.55 ± 6.85	10.46 ± 8.37	17.0 ± 19.9
Wolf Piezolith 2200	4.67 ± 1.74	5.59 ± 2.74	12.51 ± 8.37

sedatives. The majority of patients required one treatment, but in 10 patients further sessions were necessary to completely fragment the stones. The average number of shock waves for each session was 2,346 ± 634 (range 1,000–3,500) at a mean of 20.8 ± 1.3 kV (range 18–24). Patients undergoing secondary treatment received a mean of 5,745 ± 1,726 shocks in 2 or 3 treatment sessions (range 3,400–8,850).

Treatment by piezoelectric lithotripter was performed without sedation. Stone disintegration was performed at level 4 of shock wave intensity with a continuous pulse operation of 1–3 pulses per s. The mean number of impulses per session was 4,730 ± 1,340 (range 2,000–8,000). Repeat treatments were performed in 6 cases with a mean number of impulses 10,675 ± 1,582 (range 8,700–12,600). Secondary treatments usually were performed after a week.

The stones were 1 cm or less in diameter in 19 patients treated by modified Dornier HM3, between 1 and 2 cm in 20 patients, 2 cm or more in 11 patients: the number of shock waves averaged 2,231 ± 923, 3,040 ± 1,362 and 5,240 ± 2,599 for each group. Of the patients treated by Wolf 25 had stones smaller than 1 cm in diameter, 7 between 1 and 2 cm and 4 larger than 2 cm: the mean number of impulses was respectively 4,532 ± 1,287, 7,457 ± 2,728 and 10,587 ± 1,931.

Blood and urinary samples were obtained on the preoperative day and 24 h after each procedure. Particularly after subsequent lithotripsies pretreatment values were compared to values after the last treatment; the intertreatment variations of NAG excretion were considered apart.

Urinary concentrations of NAG and creatinine were determined by colorimetric methods. Urinary NAG to creatinine ratio (NAG/Cr) was calculated to compensate for the effect of intraoperative diuresis.

Serum enzymes (CK, LDH, GOT, GPT, amylase) were measured before and after lithotripsy to study the effects of shock waves on liver, pancreas, blood cells and voluntary muscles of abdominal wall.

The differences between preoperative and postoperative values were tested with Student's *t* test.

Results

Data for serum and urinary enzymes are shown in Tables 1 and 2.

The standard deviations within each group are wide because of the many variables; stone number, size or location, number of shock waves and power of the shock wave.

There was a significant increase in the urinary NAG excreted after both ESWL using the modified Dornier HM3 and piezoelectric ESWL.

Serum CK and LDH values significantly increased after spark gap lithotripsy, but only serum CK increased after piezoelectric lithotripsy.

The highest postoperative levels of enzymes were observed in patients subjected to the highest impulse rates (over 2,600 low pressure spark gap shocks or 7,000 piezoelectric shocks).

After subsequent treatments, the increase of urinary NAG for a second or third treatment was higher than after a first treatment (Table 3). Normal values were recovered within 10 days.

Discussion

The shock wave energy applied to achieve complete stone fragmentation depends on the size and hardness of the stone.

The sensation of pain is not strictly related to destructive effects of shock waves. In fact painless lithotripsy is achieved with a low skin entry energy density. On the contrary the reduction or absence of pain does not mean a reduction of energy delivered to the stone and the surrounding renal tissue.

Therefore a study of the shock waves impact on renal tissue appeared warranted. The modified Dornier HM3 is equipped with a low pressure generator reducing the pressure in the second focus by 30%, yet a higher number of shock waves is necessary to disintegrate stones in comparison with the original generator [3].

Because of the smaller focal area of piezoelectric lithotripters more shocks are needed to produce a similar destructive effect of spark gap lithotripters [8].

The overall success rate was comparable with both first and second generation lithotripters, but the new machines achieved complete disintegration of similar stones with an additional number of shocks per session compared to the original Dornier lithotripter. At the same time the rate of secondary treatments increased.

If shock waves are less effective on the stone then a higher number of shocks will be required to produce side effects.

After ESWL with the original Dornier lithotripter a slight increase of urinary NAG excretion suggested mild renal damage in cases of more than 2,000 shocks [12].

The decrease of shock wave pressure of the modified Dornier HM3 increased the threshold of measurable renal damage to about 2,600 impulses per session. The occurrence of measurable renal damage appeared to be correlated to energy applied e.g. to shock wave number times voltage.

The comparison of bioeffects of spark gap and piezoelectric pressure waves is difficult because of their different acoustic configuration.

In fact piezoelectric waves are shorter than hydroelectric shock waves without any remaining pressure.

Moreover the small final focus might reduce the area of renal parenchyma exposed to the shock waves.

However piezoelectric extracorporeal lithotripsy causes a slight renal damage in patients subjected to high number of shocks.

In fact canine kidneys examined following piezoelectric ESWL showed intrarenal and perirenal abnormalities comparable to the alterations observed after spark gap ESWL [8].

In our experience the tissue effects of piezoelectric lithotripsy were observed over a higher number of shock waves in comparison with spark gap lithotripsy, but a higher number of piezoelectric shock waves was needed to produce a destructive effect on stones similar to spark gap shock waves.

Intrarenal and perirenal bleeding were the most significant injuries induced by both spark gap and piezoelectric ESWL.

This parenchymal bleeding causes ischemic alterations of surrounding tissues, in fact 24–36 h after ESWL vacuolated tubule cells were observed at the periphery of the bleeding area signifying the start of tubular necrosis [5]. Disruption of membrane integrity constitutes a major factor leading to irreversible cell damage from ischemia, so the release of cell enzymes signifies the presence of irreversibly damaged cells.

The urinary enzyme measurements have been used to answer the question of whether cell necrosis is present or absent.

Particularly a change of urinary NAG excretion is a highly sensitive and specific sign of renal cell necrosis.

After an acute renal tubular damage urinary NAG rises within a few hours, reaches a peak and returns to normal in 4 to 7 days.

The return to normal values of NAG excretion may be used as an indicator of the healing of the damaged tissue by cicatrization but the functional significance of these scattered areas of fibrosis is not known.

Prediction of the amount of permanent renal damage is difficult to make from the NAG urinary levels measured during the first days after treatment. In summary the early renal tubular damage after anesthesia-free ESWL is measurable by NAG excretion. We cannot actually define the significance of these injuries, but extensive follow up studies should evaluate further renal functional impairment and hypertension.

However, we stressed the importance of carefully planning the treatment of large and hard stones contemplating the possibility of alternative or combined treatments. In fact the treatment of large or hard stones may require prolonged or repeated lithotripsy to achieve stone fragmentation involving the risk of inducing a renal tubular damage.

Finally the diagnosis of underlying disorders is mandatory and the need of medical prevention has to be attentively weighed up to avoid potential hazards and complications of repeated lithotripsies for recurrent stones.

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