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ORIGINAL PAPER

Urine cytology to evaluate urinary urothelial damage of shock-wave lithotripsy

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Abstract Our aim is to study the prospective trial where urine cytology was used to detect the acute urothelial mucosal damage in patients who undergo extracorporeal shock waves lithotripsy (SWL). The study included 48 consecutive patients (28 male, 20 female) with mean age of 49.02 years (range 18–66) who were treated with SWL due to renal stones (30 patients) or upper ureter stones (18 patients). The mean calculi diameter was 12.44 mm (range 5–20). Urinary cytologic examinations were done for all patients immediately before and after SWL therapy and 10 days latter. The average numbers of transitional cells, red blood cells and myocytes were counted under 40 × magnification. In overall patients the average numbers of transitional cells at the cytologic examinations done immediately before and after SWL therapy were 1.6 and 7.53 cell/field, respectively ($p = 0.001$). The increment in transitional cells at cytologic examination after SWL was significantly influenced only by number of shock waves applied ($p = 0.003$). No muscle cell was detected in all cytologic examinations. The cytologic examinations which were done after 10 days of SWL therapy showed recovery from all cytologic abnormalities. The acute increment in number of transitional cells after the SWL is not clinically important and it is a temporary change. Urothelial lesion is limited to mucosal layer and there is no evidence of damage to basal membrane or deeper muscle layer. SWL safety on urothelial and muscular layer was demonstrated. However, evaluation of larger series with use of other lithotripters is necessary before reaching any definitive conclusions.

Keywords ESWL · Cytologic examination · Urolithiasis

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Introduction

As noninvasive treatment of modality, extracorporeal shock waves lithotripsy (SWL), has become the treatment of choice for most renal and ureter stones. Although this technology offers the potential for the noninvasive delivery of focused energy, several reports have established that some patients exhibited morphological and functional abnormalities in kidneys and neighboring organs such as lungs, liver, pancreas and intestine [1–7]. Extracorporeal SWL has either acute or long-term complications; the severe-acute complications are rare with perirenal hematomas being the most common. Also transient increases in intrarenal vascular resistance, diastolic blood pressure, and markers of tubular damage were reported after SWL for upper urinary tract stones [8–10]. Data on the long-term complications of SWL are rare and controversial. The reported development of hypertension as a late complication in some studies [8, 11, 12] could not be confirmed by others [13, 14]. Recently, the development of diabetes mellitus was proposed to be a late complication due to SWL [15]. In this prospective study, we used cytologic examination to evaluate the acute urothelial damage, which may be caused by SWL, in patients who undergo SWL due to renal or upper ureter stones.

Materials and methods

This is a prospective trial which included 48 patients (male 28, female 20) with a mean age of 49.02 years (range 18–66) who was treated with SWL for upper urinary tract calculi between July 2009 and October 2009. Thirty patients were treated for renal pelvis stones, while 18 patients had SWL for upper ureter stones. The overall average of stones diameter was 12.44 mm (range 5–20); the average stones diameters for patients with renal pelvis stones and upper ureter stones were 13.13 mm (range 10–20) and 11.3 mm (range 5–15), respectively. Data on patients are shown in Table 1. The inclusion criteria were no history of renal or ureter surgery, no stenting, no patient with sever hydronephrosis and no previous application of SWL. All patients had successful fragmentation of the stones on real-time abdominal fluoroscopy. Extracorporeal SWL was administered on standard fashion during clinical routine with all procedures on electrohaydrulic lithotripter (ELMED, Turkey). No anesthesia was given, however, Nonsteroidal anti-inflammatory drugs (NSAIDs) were administered when necessary. Treatment was started at 13 kV and the energy was increased step by step to 17 kV. The average number of shock waves was 2,383 (range 1,400–2,800). All routine pre-SWL analyses such as blood coagulation tests, urine culture, renal function tests were within normal limits. Urinary cytologic examinations were done for all patients immediately before and after SWL therapy and 10 days after stone fragmentation. To have sufficient cytologic evaluation the volume of urine sample more than 20 cc of all patients were collected after micturition (Centrifuge machine: Shandon Cytospin 4, Germany). Transitional cells were counted in five fields under 40 × magnification; starting from the highest number of transitional cells-containing-field and the average was calculated. Tri-ocular light microscope was used (Olympus BX51, Japan). Red blood cells and myocytes were counted similarly. The acute increments in transitional cells and myocytes numbers at the immediate post-SWL cytologic examinations were used as an indicator to measure urothelial mucosal damage caused by SWL. However, the cytologic examinations done after 10 days of SWL therapy were used to detect the recovery of these abnormal cytologic findings.

Statistical analysis

A Student's two-tailed paired *t* test was used to compare the numbers of transitional cells at pre- and post-immediate SWL cytologic examinations. Pearson correlation test was used to determine the factors which influence the increment of transitional cells number after SWL.

Results

There was a statistically significant increment in the average number of transitional cells after the application of SWL at the post-immediate SWL cytologic evaluation. The average numbers of transitional cells immediately before and after SWL therapy were 1.6 (range 1–4) and 7.53 (range 2–36) cell/field, respectively ($p = 0.001$). Shock waves number was the only factor which significantly correlated with the increment of transitional cells at cytologic examination after lithotripsy ($p = 0.003$). The average number of transitional cells at the post-immediate SWL therapy in patients with renal stones and upper ureter stones were 8.94 (range 2–36) and 5.2 (range 5–6) cell/field, respectively. Comparison between the cytologic findings and the clinical variables of patients with renal stones and ureter stones is shown in Table 1. No myocytes and no basement membrane elements detected in any of the cytologic examinations. The findings of the pre-SWL cytologic

Table 1 Demographic characteristics of patients with renal pelvis or ureter stones

	Patients with renal stone	Patients with ureter stone	Total
Patients (*n*)*	30	18	48
Sex (male/female)	16/14	12/6	28/20
Age average (years, range)	40.85 (18–56)	62.66 (58–66)	49.0 (18–66)
Stone diameter (average, range, mm)	13.13 (10–20)	11.3 (5–15)	12.4 (10–20)
Transitional cell at pre-SWL cytologic examination (average, cell/field)	1.56 (0–4)	1.56 (0–3)	1.66 (0–4)
Transitional cell at post-immediate SWL (average, cell/field)	8.94 (2–36)	5.2 (5–6)	7.53(2–36)
Red blood cell before SWL (average, cell/field)	4.09 (0–30)	1.6 (0–5)	3.1 (0–30)
Red blood cell after SWL (average, cell/field)	>100	<50	–
Shockwaves (average, range)	2266 (2000–2500)	2400 (1400–2800)	2383 (1400–2800)

n number of cases

examinations had shown an average number of 5 red blood cell/field (range 0–30) and the majority of the patients had no red blood cells. At post-immediate SWL cytology, there was extensive presence of red blood cells (average more than 100 cell/field), but the degree of hematuria in patients with ureter stones was significantly less (average less than 50 cells/field) (Table 1). The controlled cytologic examinations which were done after 10 days of SWL therapy revealed recovery of all cytologic findings with abnormalities and the findings became similar to that of pre-SWL cytologic examinations.

Discussion

Since its introduction in 1981, SWL has become the standard treatment option for most upper urinary tract calculi and serve as first-line therapy for most ureter and kidney stones [1, 16, 17]. Although being considered as the least invasive international treatment option for urinary calculi, SWL can lead to tissue damage of the kidney and adjacent organs. To date, it remains controversial whether renal injury caused by SWL leads to long-term morbidity. The majority of the studies reported that SWL-induced renal injury is temporary and leaves no permanent damage to renal parenchyma [18–20]. However, other studies have shown hidden damage occurring frequently after SWL [21, 22]. The damage caused by SWL is claimed to be a result of membrane permeability changes [23, 24]. Cavitation-related effects, hydrodynamic jets and free radical generation are probably responsible for this toxicity [23, 24].

In the present study, we aimed to detect any acute urothelial mucosal damage caused by SWL. To exclude any factor which may aggregate or affect urothelial damage, any patient with previous surgery, sever hydronephrosis, stenting or urinary tract infection was excluded. Because the previous surgery may cause some fibrosis and this alter the healthy mucosa thus the optimum effect of shockwaves may be under evaluated. Severe hydronephrosis may lead to movement of the small calculi during SWL application, thus the possibility of aggregating SWL effect on urothelial layer may occur. Also stenting may interfere with pathway of the shockwaves thus changing the harmful effect on urothelial layer. Similarly urinary tract infection increases the fragility of mucosa, it may aggregate the impact of shockwaves on urothelial mucosa. For each patient, three cytologic examinations were done; the pre-SWL cytologic examination was done to have baseline findings before the application of SWL, the post-immediate SWL cytolgic examination was done to evaluate the acute changes on the urothelial mucosa, basement membrane and muscular layer. The last cytologic evaluation was done to detect the extent of recovery of the abnormal cytologic findings caused by SWL application. We found statistically significant increment in the number of transitional cells and red blood cells at post-immediate cytologic examination. However, these increments were not clinically important and reversible, as the cytologic findings of the last cytologic examination revealed the absence of the transient increment of transitional cells and red blood cells. There was no evidence for the presence of the basement membrane element or muscle cell detected in the post-SWL cytologic examination, which mean that the harmful effect of SWL is limited to the mucosal layers. This is a very important issue especially in patients with ureter stones because the muscular layer of the ureter play an important role in peristaltic movements, so any damage to this layer may result in impairing of this movement and/or increasing risk of stricture formation. Kirkali et al. [25] investigated the effect of SWL on the morphology and contractility of rabbit ureter . He found that the microscopic and the functional findings clearly demonstrated that electromagnetic shock waves cause significant cellular and subcellular changes leading to decreased ureteral contraction. However, these morphological and functional changes are reversible but repeated administration of higher energies may have some clinical impact on patients undergoing in situ SWL for ureter stones [25]. Horgan et al. [26] noted increased ureteral peristalsis after SWL with electromagnetic shock waves in 16 patients and attributed this observation to increased release of thromboxane B2 and prostaglandin F1ά Whether SWL increases or decreases the peristaltic movement of ureter this is an important issue and should be heavily investigated in human models. The detection of myocytes in the cytologic examination after SWL, although not enough to ascertain the damage to muscular layer, can be an indicator for possible harmful effect of SWL on muscular layer, thus alteration in parestaltic movement may be expected. Similarly, the absence of myocytes at cytologic examination is not enough to completely rule out any effect on muscular layer, but the impairment of peristaltic movement is less likely to occur. Therefore, we believe that to verify the effect of SWL on the ureter, further studies are needed because it is logical that if the SWL have harmful effect on the muscular layer, although transient increment of contractility of the ureter may occur, impairment of peristaltic movement is more likely to occur.

In our study, the post-immediate SWL cytologic findings for patients with ureter stones and renal stones showed significant variations in terms of red blood cells and small difference in the numbers of transitional cells. This is an expected finding, because in renal stones bleeding from renal parenchyma due to shock waves induced effect is common. The average number of transitional cells in patients with ureter calculi was less than in patients with renal calculi although the mean numbers of shock waves were similar. This may be due to the small size of calculi and the mobility of the target in patients with ureter stones, thus difficulty of focusing energy occurred. Therefore, less injury to the ureter urothelial layer may occur.

The number of transitional cells after lithotripsy was significantly correlated with the number of shock waves applied. Therefore, we have to be careful in application of SWL and avoid unnecessary high number of shockwaves. We believed that further studies are needed to define the harmless range of wave numbers. High number of transitional cells was also observed in conjunction with high number of inflammatory cells (neutrophils, eosinophils and macrophages); we found that 8 patients (7 of them with renal stones) had more than 10 inflammatory cell/field at post-immediate cytologic examination and the average number of transitional cells in these patients was 11.87 cell/field in comparison to 6.66 cell/field average for the remaining patients. This means that inflammatory process in the urinary system may have impact on the SWL-induced urothelial lesion. Therefore, although the presence of urinary tract infections and administration of antibiotics are debatable issue in patients who undergo SWL therapy, we do recommend a negative urine culture and administration of appropriate medical therapy prior to SWL application if the urine culture is positive.

The last cytologic examination revealed recovery of all abnormalities at the post-immediate cytologic examination, thus these changes are reversible. As a result SWL leads to significant transient increments in numbers of some cells like transitional cells and red blood cells at cytologic examination, but the increments are clinically unimportant and reversible. In the light of these findings, although SWL seems to have no crucial damage to urothelial layer, still further studies in the human models including direct microscopic examination of urolthelial and muscular layers should be done, thus acute and long-term effects of SWL can be evaluated especially in patients with ureter stones. Furthermore we should not forget that high number of sessions, short interval between sessions, high number of shock waves with high focusing, high energy, presence of infection and obstruction may mark urothelial layer damage and cause more significant deleterious effect.

Conclusion

The acute increments in the numbers of transitional cells and red blood cells after SWL therapy are statistically significant, but it is not clinically important and it is a temporary change. SWL-induced urinary urothelial lesion is limited to the mucosal layer and there is no evidence of damage to basal membrane or deeper muscle layer, thus impairment of peristaltic movement of the ureter is not expected. However, further studies in human models including direct microscopic evaluation of urothelial layer, taking the factors into account which may mark SWL damage, are required to evaluate the long-term effects of SWL on urothelial layer especially in patients with ureter stones.

References

1. Drach GW, Dretler S, Fair W, Finlayson B, Gillenwater J, Griffith D et al (1986) Report of United state cooperative study of extracorporeal shock wave lithotripsy. J Urol 135:1127–1133
2. Lingeman JE, Woods J, Toth PH, Evan AP, McAteer JA et al (1989) The role of lithotripsy and its side effects. J Urol 141:793–797
3. Etzkorn KP, Mihalov M, Brown RD, Bavishi D (1996) Colonic injury after ESWL of renal calculi. Gastrointest Endosc 44:511
4. Weber C, Moren EM, Eldon JB, Drach GW (1992) Injury of rat renal vessels following extracorporeal shock wave treatment. J Urol 147:476–481
5. Gunasekaran S, Donovan JM, Chvapil M, Drach GW (1989) Effects of extracorporeal shock waves lithotripsy on the structure and function of rabbit kidney. J Urol 141:1250–1254
6. Lingeman JE, Smith LH, Newman DM (1989) Bioeffects and long term results of ESWL. In: Lingeman JE, Newman DM (eds) Urinary calculi. Lea and Febiger, Philadelphia, p 273
7. Assimos DG, Boyce WH, Furr EG et al (1992) Urinary enzyme level after extracorporeal shock wave lithotripsy. J Urol 148:1000–1006
8. Lingean JE, Woods JR, Toth PD (1990) Blood pressure changes following extracorporeal shock waves lithotripsy and other forms of treatment for nephrolithiasis. JAMA 263:1789–1794
9. Aoki Y, Ishitoya S, Okubo K, Okada T, Maekawa S, Maeda H et al (1999) Changes in resistive index following extracorporeal shock wave lithotripsy. Int J Urol 6:483–492
10. Karlin GS, Schulsinger D, Urivetsky M, Smith AD (1990) Absence of persisting parenchymal damage after extracorporeal shock wave lithotripsy as judged by excretion of renal tubular enzyme. J Urol 144:13–14
11. Janestschek G, Frauscher F, Knapp R, Höfle G, Peschel R, Bartsch G (1997) New onset hypertension after extracorporeal shock waves lithotripsy. Age related incidence and prediction by intrarenal resistive index. J Urol 158:346–351
12. Montgomery BS, Cole RS, Palfery EL, Shuttleworth KE (1989) Does extracorporeal shock waves lithotripsy cause renal hypertension ? Br J Urol 64:567–571
13. Jewett MA, Bombardier C, Logan AG, Psihramis KE, Wesley-James T, Mahoney JE et al (1989) A randomized controlled trail to asses the incidence of new onset hypertension in patients after shockwave lithotripsy for asymptomatic renal calculi. J Urol 160:1241–1243
14. Elves AW, Tilling K, Menezes P, Wills M, Rao PN, Feneley RC (2000) Early observation of the effect of extracorporeal shock waves lithotripsy on blood pressure: prospective randomized control clinical trial. BJU Int 85:611–615
15. Krambeck AE, Gettman MT, Rohlinger AL, Lohse CM, Patterson DE, Segura JW (2006) Diabetus mellitus and hypertension associated with shock waves lithotripsy of renal and proximal ureteral stones at 19 years follow up. J Urol 175:1742–1747
16. Chaussy C, Schmeidt E, Jocham D, Brendel W, Forssmann B, Walther V (2002) First clinical experience with extra corporeally induced destruction of kidney stones waves 1981. J Urol 167:844–847
17. Tiselius H, Alken P, Buck C, Gallucci M, Knoll T, Sarica K et al (2008) Guidelines on urolithiasis: Active removal of stones in kidney. EUA Guidelines 7(6):47

18. Lottmann HB, Archambaud F, Taxer O, Mercier-Pageyral B, Helal B (2000) The efficacy and parenchymal consequences of extracorporeal shock wave lithotripsy in infants. BJU Int 85(3):311–315
19. Taxer O, Lottmann H, Archambaud F, Helal B, Mercier Pageyral B (1998) Long-term evaluation with DMSA-Tc99 m scintigarphy of renal parenchymal involvement in children after shockwave extracorporeal lithotripsy. Prog Urol 8(4):502–506
20. Brinkmann OA, Griehl A, Kuwertz-Broking E, Bulla M, Hertle L (2001) Extracorporeal shock wave lithotripsy in children. Efficacy, complications and long term follow-up. Eur Urol 39(5):591–597
21. Kaude JV, Williams CM, Milner MR et al (1985) Renal morphology and function immediately after extracorporeal shock waves lithotripsy. AJR Am J Roentgenol 145:305
22. Rubin JI, Arger PH, Pollack HM, Banner MP, Coleman BG, Mintz MC et al (1987) Kidney changes after extracorporeal shock waves lithotripsy. CT evaluation Radiol 162:21–24
23. Morgan TR, Laudone VP, Heston WD, Zeitz L, Fair WR (1988) Free radical production by high energy shock waves-comparison with ionizing irradiation. J Urol 139:186–189
24. Crum LA (1988) Cavitations microjects as a contributory mechanism for renal calculi disintegration in ESWL. J Urol 140:1587–1590
25. Kirkali Z, Esen AA, Hayran AM, Gencbay A, Gidener S, Güven H et al (1995) The effect of extracorporeal electromagnetic shock waves on the morphology and contractility of rabbit ureter. J Urol 154:1939–1943
26. Horgan PG, Hanley D, Burke J, Couse NF, Fitzpatrick JM (1993) Extracorporeal shock wave lithotripsy induced the release of prostaglandins which increase ureteric peristalsis. Br J Urol 71:648–652