Research Paper

Effect of Diuretic and Stone Removal Mixture on Kidney Stones and its Influence on Renal Function and Urinary Levels

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Our main objective is to study the effect of diuretic Paishi mixture on renal calculus after extracorporeal shock wave lithotripsy and its effect on renal function and urinary N-acetyl-beta-d-glucosaminidase, beta-2 microglobulin, cystatin C levels. A total of 150 patients with kidney stones undergoing extracorporeal shock wave surgery were randomly divided into research group and control group with 75 subjects in each group. The patients in the control group were treated with routine methods such as anti-infection, pain relief and hemostasis after operation, while the research group was treated with diuretic and stone-dispelling mixture on the basis of the control group. The medication cycle is 7 d. The treatment effects, symptom scores, average time for residual stone removal, renal function-related indicators, urine N-acetyl-beta-d-glucosaminidase, beta-2 microglobulin, cystatin C levels, inflammatory factor levels and the proportion of analgesic drugs were compared between the two groups. The drug effect of the study group was better than that of the control group ($p<0.05$), the symptom score, average time of residual stone excretion, levels of renal function indicators, blood creatinine and blood urea nitrogen in the study group were lower than those of the control group ($p<0.05$). The levels of urinary N-acetyl-beta-d-glucosaminidase, beta-2 microglobulin and cystatin C in the study group were better than those in the control group ($p<0.05$). The indicators of inflammatory factors and usage rate of analgesic drugs in the study group were lower than those in the control group ($p<0.05$). Diuretic and stone removal mixture can significantly improve the postoperative effect of extracorporeal shock wave lithotripsy, shorten the time of stone removal, increase the levels of renal function, urinary N-acetyl-beta-d-glucosaminidase, beta-2 microglobulin, cystatin C, etc., improve the level of inflammatory factors and reduce the usage rate of analgesic drugs.

Key words: Diuretic, stone removal mixture, renal function, analgesic drugs, kidney stones

Kidney stones are one of the common diseases of the urinary system. China is one of the countries with high incidence of kidney stones in the world. According to an epidemiological survey, the prevalence of kidney stones in Chinese adults is 5.8 % and the prevalence rate of men is higher than that of women[1]. Kidney stones are related to lifestyle, eating habits, drinking water and other factors. Kidney stones may lead to urinary tract infection, hematuria and obstruction during stone passage, which may even cause serious consequences such as hydronephrosis and renal failure[2]. Therefore, it is necessary to study the drug regimen for kidney stones. Clinically, Extracorporeal Shock Wave Lithotripsy (ESWL) is mostly used in the treatment of kidney stones. ESWL is widely used due to its advantages of non-invasiveness, low cost and no need for anesthesia. However, ESWL faces problems such as kidney damage and its low effectiveness of stone removal, which has attracted widespread attention from researchers. Therefore, how to use drugs after ESWL has become a new research hotspot. In this study, diuretic and calculus-dispelling mixture was used after ESWL to study the effect of the drug on the elimination of residual stones and the assessment of multiple indicators such as renal function. The main ingredients of diuretic and calculus-removing mixture are green bark, Lysimachiae Herba, Shi Wei, cumin, Spora Lygodii, knotweed, endothelium corneum gigeriae galli, Wang Bu Liu Xing (Chao) and so on.

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MATERIALS AND METHODS

General information:

The 150 subjects in this study were all ESWL patients with kidney stones admitted to Nanjing First Hospital from January 2021 to January 2022. There were 75 patients in the research group, 40 males and 35 females with an average age of 41.28±4.36 y and an average disease duration of 7.24±1.18 mo, including 9 patients with recurrent kidney stones and the average stone diameter is 14.96±2.76 mm. Stones are located in the left side of the kidney in 38 patients and on the right side in 37 patients. There were 75 patients in the control group, 41 males and 34 females with an average age of 41.32±4.35 y and an average course of disease of 7.25±1.19 mo, including 10 patients with recurrence of kidney stones and the average diameter of kidney stones was 14.97±2.75 mm. Stones are located in the left side of the kidney in 37 patients and on the right side in 38 patients. There was no significant difference in the basic data between the two groups ($p>0.05$).

Inclusion and exclusion criteria:

Inclusion criteria: Patients should meet the diagnostic criteria for kidney stones in the "Guidelines for the Diagnosis and Treatment of Urological Diseases in China"; the diameter of the stones is 5-20 mm; the age is 20-65 y old; all the patients understood the purpose of this study and signed the informed consent.

Exclusion criteria: Patients with poor compliance, mental disorders and those who do not cooperate with treatment; patients with ureteral stenosis, ureteral obstruction and congenital ureteral malformations; patients with renal function diseases; those who have recently received Calcium (Ca^{2+}) antagonists and patients with serious diseases are excluded from the study.

Research methods:

Control group: ESWL was performed after conducting basic preoperative examinations. Before lithotripsy, patients need to drink a lot of water. It is generally recommended to drink 500 ml of water 30 min before surgery. Patients are required to drink more than 2000 ml of water after surgery. The patient took tamsulosin hydrochloride sustained-release capsules (Manufacturer: Hangzhou Kangenbei Pharmaceutical Co., Ltd., approval document: H20050285, specification: 0.2 mg×30) 0.2 mg each time, once in the morning and once in the evening continuously for 7 d after lithotripsy. During this period, some jumping exercises are performed every day to improve the discharge of residual stones.

Research group: On the basis of the control group, diuretic and calculus-dispelling mixture was added. The diuretic and calculus-removing mixture consists of 10 g each of Qingpi, Shi Wei, Qumai, *Desmodium*, pangolin, *Polygonum cuspidatum* and agarwood, 15 g each of Haijinsha, talc, endothelium corneum gigeriae galli and Wang Bu Liu Xing, 12 g of *Achyranthes bidentata* and 20 g of *Imperata* rhizome. For patients with waist and abdominal cramps, 10 g each of white peony root and licorice are added to the basic prescription. For patients with low back pain and dull pain, add 10 g each of *Eucommia* and *Psoralea*, and 15 g of Radix Dipsaci. For patients with red tongue, dry mouth and kidney yin deficiency, add 10 g each of raw *Rehmannia glutinosa* and turtle shell and 15 g of Radix *Ophiopogon japonicus*. For patients with purple tongue coating, add 10 g each of peach kernels and saponins and 15 g of safflower. Diuretic and calculus-dispelling mixture is decocted with water, one dose per day, once in the morning and evening, 400 ml each time and the medication cycle is 7 d.

Research assessment indicators:

Treatment effect evaluation criteria: The treatment effect was evaluated and divided into three categories-healed, effective, ineffective. Healed category means that the stone was discharged and stone samples were obtained, Computed Tomography (CT) results showed that the shadow of the stone disappeared completely, the obstruction was relieved and there was no hydronephrosis. Effective category showed symptoms like kidney stones can pass through the first stenosis smoothly and enter the upper part of the ureter, most of the multiple stones can be discharged, hydronephrosis at the site of the stones is significantly reduced, CT results showed that the shadow of the stones is significantly reduced. Ineffective category showed symptoms such as the stones did not become smaller, the CT results showed that the shadow of the stones did not change, the hydronephrosis did not decrease significantly and the urinary system infection still existed.

Total effective rate=Recovery rate+effective rate.

Assessment and evaluation criteria for each index: Symptoms are divided into hematuria, frequent urination, urgency and dysuria, abdominal and perineal pain, tenderness or percussion pain and abnormal urination. The full symptom score for each item is 3 points with 0 points for no symptoms, 1 point for mild symptoms, 2 points for moderate symptoms and 3 points for severe symptoms.

Evaluation of residual stone discharge is necessary to evaluate the duration of stone expulsion and the disappearance time of stone expulsion pain. The pain level was evaluated by the stone removal pain Visual Analog Scale (VAS) score, with a full score of 10 points. No pain is scored as 0 points, mild pain is scored as 1-3 points, severe pain is scored as 4-6 points, severe pain and sleep disturbance is scored as 7-10 points. A VAS score of 3 or less was considered as pain-free.

Evaluation of renal function related indicators mainly assesses the levels of Serum creatinine (Scr) and Blood Urea Nitrogen (BUN). After treatment, the lower the levels of Scr and BUN, the higher the level of renal function.

After treatment, the lower the levels of urinary N-Acetyl-beta-d-Glucosaminidase (NAG), beta-2 Microglobulin (β_2-MG), Cystatin C (CysC) in urine, then the better its therapeutic effect.

The levels of inflammatory factors and the proportion of analgesic drugs used are evaluated. Inflammatory factors were mainly evaluated for the levels of high sensitivity C-Reactive Protein (hs-CRP), Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). The lower the value of these three levels before treatment, the better the improvement effect of inflammatory factors. The proportion of analgesic drug usage mainly focuses on the number of patients require analgesic drug. The lower the number of patients, the lower the proportions of analgesic drug use.

Statistical analysis:

Data processing in this study was processed by Statistical Package for the Social Sciences (SPSS) 22.0 software, t or χ^2 test was used for comparison between groups and $p<0.05$ was considered statistically significant in the difference.

RESULTS AND DISCUSSION

Potential Total effective rate was compared between the two groups as shown in Table 1. After treatment, the total effective rate was 100 % in the study group and 85.33 % in the control group and there was a significant difference between the two groups ($p<0.05$).

Symptom score were compared between the two groups as shown in Table 2. Before treatment, there was no significant difference in the scores of symptoms and indicators between the two groups ($p>0.05$). After treatment, the scores of symptoms in the study group were significantly lower than those in the control group ($p<0.05$).

TABLE 1: COMPARISON OF THE TOTAL EFFECTIVE RATE BETWEEN THE TWO GROUPS OF PATIENTS ($\bar{x}\pm s$)

Group	n	Healed	Effective	Ineffective	Total effective rate
Research	75	64 (85.33 %)	11 (14.67 %)	0	100 %
Control	75	52 (69.33 %)	12 (16 %)	11 (14.67 %)	85.33 %
χ^2					8.27
p					<0.05

TABLE 2: COMPARISON OF SYMPTOM SCORES BETWEEN THE TWO GROUPS OF PATIENTS (POINTS, $\bar{x}\pm s$)

Group	n	Time	Hematuria	Frequent urination	Urgency and dysuria	Abdominal and perineal pain	Tenderness or percussion pain	Abnormal urination
Research	75	Before treatment	2.01±0.09	2.11±0.11	2.12±0.12	2.13±0.12	2.16±0.13	2.15±0.13
		After treatment	0.22±0.03^{b1}	0.32±0.05^{b1}	0.28±0.04^{b1}	0.19±0.03^{b1}	0.21±0.04^{b1}	0.16±0.03^{b1}
Control	75	Before treatment	2.02±0.09	2.1±0.11	2.12±0.12	2.13±0.11	2.16±0.12	2.15±0.14
		After treatment	0.81±0.11^{b}	0.94±0.09^{b}	0.92±0.08^{b}	0.68±0.05^{b}	0.69±0.08^{b}	0.79±0.09^{b}

Note: $^{b}p<0.05$: Compared with before treatment and $^{1}p<0.05$: Compared with the control group

Residual stone discharge time was compared between the two groups as shown in Table 3. The disappearance time of stone expulsion pain and the duration of time for stone expulsion in the study group were shorter than those in the control group ($p<0.05$).

Renal function index levels were compared between the two groups as shown in Table 4. Before treatment, there was no significant difference in the levels of Scr and BUN between the two groups ($p>0.05$). After treatment, the levels of these two indicators in the study group were significantly lower than those in the control group ($p<0.05$).

Before treatment, there was no significant difference in the levels of urinary NAG, β_2-MG, and CysC between the two groups ($p>0.05$). After treatment, the three indicators in the study group were significantly lower than those in the control group ($p<0.05$) (Table 5).

Before treatment, there was no significant difference in the three indexes of inflammatory factors between the two groups ($p>0.05$). After treatment, the three indexes of inflammatory factors in the study group were significantly lower than those in the control group ($p<0.05$) (Table 6). After the ESWL operation, 4 patients in the study group and 16 patients in the control group took analgesic drugs and there was a significant difference ($p<0.05$) (Table 7).

TABLE 3: COMPARISON OF RESIDUAL STONE DISCHARGE TIME BETWEEN THE TWO GROUPS OF PATIENTS AFTER MEDICATION (x̄±s)

Group	n	Pain duration for expulsion of residual stone	Duration for stone removal
Research	75	3.46±1.23	5.14±1.22
Control	75	7.22±1.61	8.25±1.63
t		9.285	7.582
p		<0.05	<0.05

TABLE 4: COMPARISON OF RENAL FUNCTION INDEX LEVELS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group	Scr (μmol/l)		BUN (mmol/l)	
	Before treatment	After treatment	Before treatment	After treatment
Research (n=75)	134.28±8.15	96.36±6.18	9.61±1.12	5.36±0.09
Control (n=75)	134.59±8.28	113.51±7.25	9.62±1.13	8.01±0.11
t	0.098	3.218	0.097	4.296
p	>0.05	<0.05	>0.05	<0.05

TABLE 5: COMPARISON OF URINE NAG, β_2-MG, AND CYSC LEVELS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group	n	NAG (U/l)		β_2-MG (mg/l)		CysC (mg/l)	
		0.097	0.097	0.097	0.097	0.097	0.097
Research	75	48.42±4.21	18.15±1.22	16.18±2.34	5.11±1.12	5.82±1.08	2.01±0.62
Control	75	48.53±4.22	28.62±2.53	16.12±2.33	8.24±1.91	5.83±1.09	3.16±0.82
t		0.135	3.869	0.0913	4.128	0.0725	4.865
p		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

TABLE 6: COMPARISON OF INFLAMMATORY FACTOR LEVELS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s)

Group	n	hs-CRP (mg/l)		TNF-α (μg/l)		IL-6 (ng/l)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Research	75	36.17±3.51	18.68±2.35	6.21±1.17	0.99±0.08	54.42±5.87	30.92±4.14
Control	75	36.18±3.49	9.85±1.64	6.21±1.18	2.13±0.14	54.43±5.91	40.82±5.13
t		0.142	8.136	0.0525	8.864	0.135	2.658
p		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

TABLE 7: COMPARISON OF THE PROPORTION OF ANALGESIC DRUGS USED BETWEEN THE TWO GROUPS OF PATIENTS AFTER ESWL (n, %)

Group	n	Proportion of analgesic drugs used (%)
Research	75	4 (5.33)
Control	75	16 (21.33)
χ^2		18.672
p		<0.05

ESWL uses extracorporeal shock waves to focus on human organs to pulverize human stones and excrete them through the human urinary system. The mechanism of stone crushing also causes damage to kidney tissue due to the force of the shock wave. In this study, the detailed working mechanism of ESWL and the damage to the kidney will not be studied for the time being, but the effect of diuretic and stone removal mixture on ESWL surgery will be discussed. ESWL-induced renal damage related research theory results are large in number, which shows that the study of drug protection is very important. Shock wave damage is mainly due to kidney yin, yang deficiency, qi stagnation and blood stasis[3]. Therefore, the core activity of drug is to protect and nourish the kidneys, activate blood circulation and remove blood stasis. In this research, the diuretic and calculus-dispelling mixture contained endothelium corneum gigeriae galli which can eliminate kidney calculus, Haijinsha has diuretic and calculus-dispelling effect and knotweed can dissipate blood stasis and relieve pain while green bark can promote blood circulation and dissipate stagnation. Wang Bu Liu Xing has the effect of diuresis and tonifying stranguria and pangolin can nourish qi and blood. The main effect of this basic prescription is diuresis and its main drug activity is to expel residual stones from the body by drinking a lot of water and urinating. Therefore, in this study, it was found that the residual stone removal time in the research group was significantly shorter than that of the control group, which is because of the diuretic effect of the drug. Studies have shown that *Desmodium* can inhibit the formation of calcium oxalate stones in the kidney. It not only has the effect of diuretic and stone removal, but can also supplement citric acid to reduce the saturation of calcium oxalate in urine. It contains a large number of polyphenolic compounds which can reduce oxidative stress and protect renal epithelial cells, achieve the balance of normal levels of calcium, magnesium, vanadium and other elements in the kidney and finally intervene in the formation of calcium oxalate stones in the kidney[4,5]. Some scholars have also pointed out that Haijinsha can promote the peristalsis of the ureter, increase the pressure in the upper ureter cavity and have a greater impact force during urination, which was more helpful to discharge the stones[6]. The diuretic and calculus-dispelling mixture in this study not only takes care of calculus expulsion, but also focuses on relieving pain and improving renal function in patients. Therefore, on the basis of the basic prescription, several other herbs were added. Such as white peony root, licorice root, *Eucommia ulmoides*, *Psoralea*, raw *Rehmannia* root, turtle shell, *Ophiopogon japonicus*, peach kernel, saponins and so on. *Paeoniae* Alba has the effect of slowing down pain, licorice has the effect of clearing away heat, detoxifying and relieving pain. *Eucommia* can nourish liver and kidney, strengthen bones and muscles, *Psoralea* can warm kidney and strengthen yang, softening and resolving stagnation. *Ophiopogon japonicus* can nourish yin and promote body fluid and peach kernel has the effect of promoting blood circulation and removing blood stasis. Therefore, in this study, a variety of formulas with analgesic effects included in the diuretic and stone removal mixture which made the symptoms of abdominal and perineal pain, tenderness or percussion pain and pain of stone removal in the study group significantly lighter than those in the control group. The proportion of using analgesic drugs in the study group was lower than that of the control group. In this study, the presence *Eucommia* and *Psoralea* in the diuretic and stone removal mixture are all helpful in improving the renal function of the patients. Therefore, in this study, the renal function, Scr and BUN levels of patients in the study group were better than those in the control group. *Ophiopogon japonicus*, peach kernel, saponins, etc. can nourish yin and qi, so the urine NAG, β_2-MG, and CysC levels of the patients in the study group were better than those of the control group.

Kidney stones, as a common disease, have been extensively studied. The long-term deposition of calcium oxalate crystals in the kidney can easily damage the epithelial cells of the renal tubules,

leading to inflammation, inducing a large number of reactive oxygen species and reducing the activity of superoxide dismutase[7]. This is likely to cause oxidative stress on renal epithelial cells which leads to lipid peroxidation damage and the more serious consequence is to cause apoptosis or necrosis of renal epithelial cells themselves, which aggravates the toxicity of cells, promotes the adhesion of crystals and eventually leads to the formation of kidney stones. The formation mechanism of kidney stones has not been unanimously recognized[8]. Studies have shown that oxidative stress and inflammatory injury of renal epithelial cells are the key links leading to the formation of kidney stones[9]. Studies have also shown that Phosphoinositide 3-Kinase/protein kinase B/mammalian Target of Rapamycin (P13K/Akt/mTOR) pathway plays an important role in the occurrence of kidney stones[10]. Studies have pointed out that β_2-MG is a low-molecular protein of single-chain polypeptide, which can be freely filtered in human glomerulus and the renal tubules can absorb most of β_2-MG[11]. But when there is a problem with renal function, β_2-MG is difficult to be reabsorbed by the renal tubules, so it is directly excreted from the urine. Therefore, detecting the level of β_2-MG in urine is often an important indicator to measure renal function. hs-CRP and TNF-α are important mediators of inflammation, both of which can reflect the level of inflammation in the human body, while IL-6 is a cytokine produced by various cells, which can promote the aggravation of body damage. The increase of hs-CRP, TNF-α and IL-6 levels will easily increase the burden of damage to the body. Studies have shown that Sanjin Paishi decoction can reduce the inflammatory response of the human body and improve renal function[12]. Sanjin Paishi decoction is similar to the diuretic paishi mixture in this study. Modern pharmacological studies have proved that the main components of *Desmodium* are flavonoids, which can coordinate with calcium ions in urine, thereby inhibiting the deposition and growth of calcium oxalate crystals[13]. Similarly, modern pharmacological research has also proved that Wang Bu Liu Xing contains imidazole antibiotics and its nitro group can reduce the amino group in an oxygen-free environment in the cell, which can inhibit the synthesis of bacterial Deoxyribonucleic Acid (DNA), thereby achieving the effect of anti-anaerobic bacteria[14]. So this explains that after medication, the levels of inflammatory factors in the study group patients are lower than that in the control group.

Studies have shown that CysC is not affected by many different factors such as physiology and inflammation and its content in the human body is almost constant and it is extremely sensitive to damage to kidney function. When the kidney is damaged, the CysC value will increase[15]. In clinical research, CysC is often used as the gold standard for evaluating renal function. Studies have shown that Yishen Paishi mixture can reduce CysC value and improve renal function[16]. Yishen Paishi mixture is mainly composed of *Rehmannia glutinosa*, dodder seed, *Plantago* seed, *Cistanche*, etc., and its function of benefiting kidney and nourishing yang is similar to that of diuretic and Paishi mixture in this study. This shows that diuretic and stone removal mixture can stabilize CysC value and improve renal function level. This study has certain limitations such as the urine volume of the patients was not studied. Diuretic Paishi granules have a diuretic effect. However, after taking diuretic Paishi granules, the important research index was the daily urine output index. In addition, the drug idea mentioned in this study is to expel residual stones from the body by drinking a lot of water and subsequent urination. But the study ignored the important indicator of daily water intake in both the study group and control group. In follow-up studies, researchers should pay close attention to these two indicators.

In this study, the patients in the study group had a good drug effect, which could effectively improve the renal function of the patients, reduce the level of inflammation, relieve the pain of the patients and reduce the proportion of analgesic drugs usage, which is worthy of widespread recommendation for drug use.

Author's contribution:

Shengli Zhang and Wei Chen contributed equally to this work and should be considered co-first authors.

Funding:

This work was supported by National Natural Science Foundation of China (Grant No. 92049111 and 81570613) and Jiangsu Provincial Social Development Project (Grant No. BE201761).

Conflict of interests:

The authors declared no conflict of interest.

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This article was originally published in a special issue, "Transformative Discoveries in Biomedical and Pharmaceutical Research" Indian J Pharm Sci 2023:85(4) Spl Issue "270-276"