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ORIGINAL PAPER

The protective effects of the traditional Chinese herbs against renal damage induced by extracorporeal shock wave lithotripsy: a clinical study

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Abstract Extracorporeal shock wave lithotripsy (ESWL)-induced renal damage can occur as a result of multiple mechanisms. We have reported previously that Astragalus membranaceus, Salvia miltiorrhiza, a decoction of six drugs containing rhizoma Rehmanniae preparata and supplements of a few traditional Chinese medicinal herbs for invigorating the kidney and excreting calculus, have a protective effect on renal injury induced by high-energy shock waves (HESW) in rabbits. In this clinical study we further investigate the protective effects of these traditional Chinese herbs against renal damage induced by ESWL. Sixty consenting patients with renal calculus who underwent ESWL treatment were included and randomly assigned to the medication group or control group. Post-ESWL plasma nitric oxide (NO), endothelin-1 (ET-1), malondialdehyde (MDA), and serum tumor necrosis factor α (TNF-α) increased significantly in the controls ($P < 0.05$), while in the medication group, slightly but not significantly elevated levels of plasma ET-1, NO, and serum TNF-α were found. The difference between the groups was statistically significant ($P < 0.05$). The levels of superoxide dismutase (SOD) decreased gradually in the controls, reaching a trough 72 h after ESWL ($P < 0.05$), while in the treated group it was unchanged, and remained at a level higher versus the controls ($P < 0.05$). Plasma NO peaked twice by 72 h and at 1 week in the controls ($P < 0.05$). Urinary enzymes and β_2-microglobulin increased significantly and peaked by 24 h and immediately after ESWL ($P < 0.05$). These values were greater in the controls, and the difference was statistically significant ($P < 0.05$). This study demonstrates that the preparations of traditional Chinese medicines for invigorating the kidney and excreting calculus can reduce renal tubular damage induced by ESWL, and can shorten the recovery time of renal tubules in human subjects.

Keywords Extracorporeal shock wave lithotripsy · Renal injury · Calculus · Chinese traditional medicines

Introduction

Clinical introduction of extracorporeal shock wave lithotripsy (ESWL) has revolutionized treatment of renal calculi. Effective and reliable, ESWL has become the treatment of choice in symptomatic urinary calculi. Although it is markedly effective, the application of high-energy shock waves (HESW) has not been found to be completely safe and free of side effects. Today, it is well known that some acute and chronic side effects may be encountered any time after HESW application [1]. Apart from local hematomas and a potential risk for hypertension, alterations in kidney function have been reported. A transient increased excretion of small molecular proteins (β_2-microglobulin) and enzymes (e.g., *N*-acetyl-beta-D-glucosaminidase) was described, following ESWL, as signs of proximal tubular impairment [2, 3].

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Initially, the bioeffects of shock wave lithotripsy were attributed mainly to the direct effect of the shock wave energy. More recently, oxygen-free radical production related to ischemia/reperfusion after ESWL is believed to contribute to parenchymal damage via lipid peroxidation and the disruption of cellular membranes [4]. In order to lessen the degree of renal injury caused by ESWL, various pharmacologic agents have been evaluated to preserve renal morphology and function. Among these agents, verapamil, an organ-protective calcium antagonist, has an excellent stabilizing effect on postischemic malperfusion, and has been found to be beneficial in this respect [5].

Many traditional Chinese medicines have been proven to be effective in decreasing ischemia/reperfusion injury of organs including brain, heart, and kidney. We have reported previously that Astragalus membranaceus and Salvia miltiorrhiza have a protective effect on renal injury induced by HESW in rabbits [6, 7]. Moreover, we have found that a decoction of six drugs containing rhizoma Rehmanniae preparata and supplements of a few traditional Chinese medicinal herbs for invigorating the kidney and excreting calculus, limited the renal injury induced by ESWL in the rabbit [8]. A decoction of six drugs containing rhizoma Rehmanniae preparata is a classic recipe to protect the kidney, as described by Qian Yi, a specialist in traditional Chinese medical science of the North Song Dynasty 1,000 years ago. It was derived from the Jingui decoction for invigoration of kidney energy by Zhang Zhongjing who was an expert in traditional Chinese medical science in the Han dynasty 2,000 years ago in China [9].

Rhizoma Rehmanniae preparata has been widely used to treat many renal diseases, and has been proven to be quite safe. It is easy to obtain and inexpensive. In the study, we adjusted the formulation to decrease adverse reactions according to our prior results in the rabbit models and the prior clinical study in which we had chosen ten healthy volunteers to investigate the side effects. We aimed to investigate the potential protective effect of this medication against shock-wave-induced impairment of renal tubular function in humans.

Methods

Subjects

Between December 2002 and May 2007, 60 consenting patients with renal calculus who underwent the initial ESWL treatment and who fulfilled the following criteria were included: age 23–65 years (mean age 41.8 years), pelvic or calyceal stones of less than 20 mm, creatinine level of less than 133 μmol/L, no evidence of obstruction on excretory urogram, no conspicuous hydronephrosis, no auxiliary measures before or after ESWL, no infusion of contrast medium during ESWL, no contraindication to the materials, and no anesthesia. Each patient was treated for a solitary calculus, and had no additional stones in the treated kidney. No patient was treated for a staghorn calculus. All of the subjects signed informed consent documents prior to participation. Studies were performed in accordance with the ethical standards as originally laid down in the 1964 Declaration of Helsinki and updated in October 2001, Table 1.

Protocol

These patients were randomly assigned to the medication group ($N = 30$) or control group ($N = 30$). Patients of the control group received no medication. The patients of the medication group underwent treatment with the traditional Chinese medicines for 7 days starting from 3 days before ESWL. The preparations comprised 11 herbs including common yam rhizome (Rhizoma Diocoreae, *Shanyao*, 24 g), Rehmannia dried rhizome (Radix Rehmanniae, *shengdi*, 15 g), Asiatic Cornelian cherry fruit (Fructus Corni, *shanzhuyu*, 9 g), Oriental water plantain rhizoma (Rhizoma Alismatis, *zexie*, 9 g), Indian bread (Poria, *fuling*, 9 g), Root-bark of peony (Cortex Moutan, *danpi*, 9 g), Astragalus membranaceus (Radix Astragali, *huangqi*, 18 g), Asiatic plantain herb (Herba Plantaginis, *cheqiancao*, 9 g), Lalang grass rhizome (Rhizoma Imperatae, *baimaogen*, 15 g), Christina loosestrife (Herba Lysimachiae, *jinqiancao*, 15 g) and Spora lygodii (Lygodium, *haijinsha*, 4.5 g). Each preparation was decocted to 300 ml. In the treated group, each participant received 150 ml orally twice daily.

Each patient received 2,000 shock waves during 30–45 min in a MZ-V lithotriptor with an electromagnetic wave generator at 16 kV. The lithotriptor, type M-Z ESWL-V, is manufactured by the Huikang Medical Apparatus Co. Ltd., Shenzhen, China. X-ray studies were used to localize the kidney stones. The indication for treatment after ESWL was evidence of hydronephrosis secondary to an obstructing renal pelvic stone on renal sonography.

Biochemical parameters

Blood was collected (10 ml) from the median cubital vein of each patient before and immediately after ESWL, at 24

Table 1 Patient characteristics

	Sex		Stone location			
	M	F	Upper calyx	Middle calyx	Lower calyx	Renal pelvis
Control	20	10	2	3	5	20
Medicated	19	11	5	4	6	15

and 72 h, and on day 7. Urine was collected before and at 24 and 72 h, and on day 7 after ESWL. A research technician instructed patients in the proper technique and timing of collection, and assured that samples were delivered promptly to the laboratory. The blood and urine samples were maintained at −20°C. The blood was prepared for nitric oxide (NO), endothelin-1 (ET-1), tumor necrosis factor α (TNF-α), superoxide dismutase (SOD), and malondialdehyde (MDA) levels, and the urine for *N*-acetyl-β-D-glucosaminidase (NAG), γ-glutamyltransferase (γ-GT), β_2-microglobulin (β_2-MG), and creatinine. We measured pre- and post-ESWL plasma NO, SOD, MDA and ET-1, serum TNF-α, urinary NAG, γ-GT, β_2-MG, and creatinine.

Plasma ET-1, serum TNF-α, and urine β_2-MG levels were determined by radioimmunoassay [10]. SOD activity and MDA levels were measured by biochemical spectrophotometric analysis according to the manufacturer's instructions, and quantified by using a spectrophotometer [6]. NAG and γ-GT were measured by colorimetric assay according to Li et al. [2]. Creatinine was measured by a creatine analyzer. The investigator examining all kidney specimens was blinded as to the specific group of each patient.

Assessment of major adverse reactions

Lumbodynia, gross hematuria, and adverse reactions of medication were assessed.

Statistical methods

The results of laboratory examination are presented as mean values ± standard error of the mean (SEM, $n = 30$ patients/group). Statistical analysis was performed by one-way ANOVA utilizing post-hoc Dunnett. Data of clinical by-effective assessment and effect of stone elimination in the medication and control groups were compared using Pearson's Chi-square test. All statistical analyses were performed using computer software (13.0, SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered to indicate statistical significance in all analyses.

Results

Changes of plasma ET-1, NO and serum TNF-α levels

Before ESWL, plasma ET-1, NO, and serum TNF-α levels were not significantly different between the two groups ($P > 0.05$). In the control group, post-ESWL plasma ET-1 and serum TNF-α levels increased significantly at 24 h ($P < 0.05$), and plasma NO levels increased significantly at 24 h and at week 1. The index showed no significant increase in the medication group ($P > 0.05$), and was significantly lower than it was in the control group ($P < 0.05$, Table 2, Figs. 1, 2, 3).

Changes of plasma SOD and MDA levels

Before ESWL, plasma SOD and MDA levels were not significantly different between the two groups ($P > 0.05$). In the

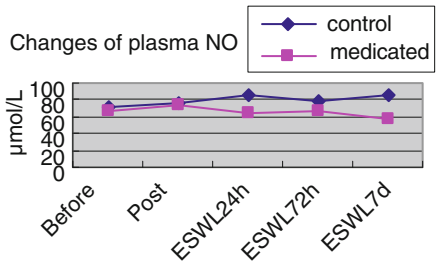

Fig. 1 Changes of plasma NO (μmol/L)

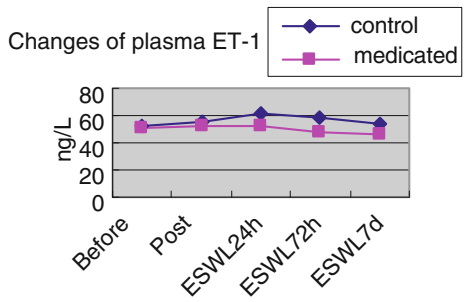

Fig. 2 Changes of plasma ET-1 (ng/L)

Table 2 Mean and standard deviations of plasma ET-1(ng/L), NO (μmol/L), and serum TNF-α (μg/L) before and after ESWL (mean ± SD)

	Plasma NO		Plasma ET-1		Serum TNF-α	
	Control ($n = 30$)	Medicated ($n = 30$)	Control ($n = 30$)	Medicated ($n = 30$)	Control ($n = 30$)	Medicated ($n = 30$)
Before	71.69 ± 27.17	67.31 ± 33.55	52.11 ± 12.95	51.02 ± 6.18	1.87 ± 0.33	1.81 ± 0.56
Post	76.73 ± 41.65	72.81 ± 35.32	55.17 ± 11.94	52.71 ± 11.33	2.35 ± 0.522	1.90 ± 0.63
ESWL24 h	84.85 ± 25.44[a]	64.57 ± 28.37[b]	61.78 ± 10.87[a]	52.98 ± 16.61[b]	2.67 ± 0.32[a]	1.89 ± 0.55[b]
ESWL72 h	79.59 ± 26.36	67.14 ± 28.68	58.81 ± 13.46[a]	48.44 ± 10.65[b]	2.49 ± 0.32[a]	1.91 ± 0.54[b]
ESWL7d	86.86 ± 36.08[a]	56.96 ± 22.43[b]	54.53 ± 10.21	46.43 ± 8.26[b]	2.37 ± 0.53[a]	1.8 ± 0.56[b]

[a] $P < 0.05$ indicates pre- versus post-ESWL

[b] $P < 0.05$ indicates control versus medicated

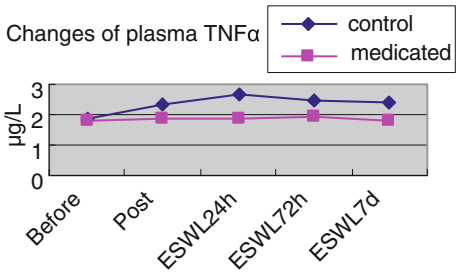

Fig. 3 Changes of plasma TNFα (μg/L)

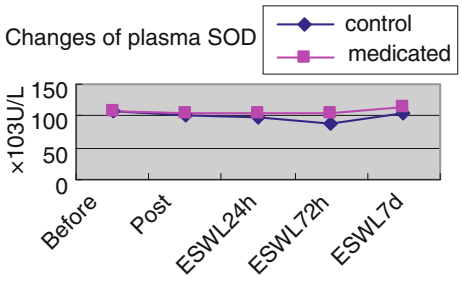

Fig. 4 Changes of plasma SOD ($\times 10^3$ U/L)

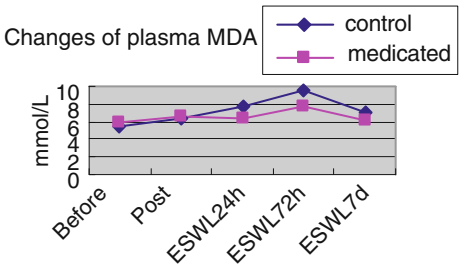

Fig. 5 Changes of plasma MDA (mmol/L)

control group, SOD values post-ESWL showed a significant decrease, and reached the lowest levels at 72 h ($P < 0.05$) and increased to baseline by 1 week. SOD levels in the medication group showed no significant decrease ($P > 0.05$), and were significantly higher when compared with the controls at 72 h and at 1 week ($P < 0.05$). Post-ESWL plasma MDA in the both groups showed a significant increase and peaked by 72 h ($P < 0.05$). But MDA levels in the medication group showed a greatly lower increase versus the controls at 24 and 72 h ($P < 0.05$, Table 3; Figs. 4, 5).

Changes of urine NAG, γ-GT and β_2-MG levels

Before ESWL, urine NAG, γ-GT, and β_2-MG levels were not significantly different between the two groups ($P > 0.05$). The urine enzyme activities, γ-GT and NAG, reached the highest levels at 24 h in the control group ($P < 0.05$), and decreased to baseline by 72 h and 1 week, respectively ($P > 0.05$). Urine β_2-MG levels reached the highest levels immediately in the control group ($P < 0.05$), and decreased to baseline by 24 h ($P > 0.05$). The peak values and γ-GT levels at 24 h were significantly higher than the values at the same time points in the medication group ($P < 0.05$), while urine NAG, γ-GT, and β_2-MG reached the highest values immediately after ESWL in the medication group, respectively ($P > 0.05$, Table 4, Figs. 6, 7, 8).

Effect of stone elimination

Though both the groups achieved quite a good effect in ESWL, the medication group (with a stone-free rate of 83.3%) had a much higher rate of curing than did the controls (with a curing rate of 60.0%). In addition, there was a significant difference between the two groups ($X^2 = 4.02$, $P < 0.05$). In addition, 7 patients in the medication group and 16 in the controls had to undergo re-ESWL. The difference was also significant between the two groups ($X^2 = 5.71$, $P < 0.05$, Table 5).

Major adverse reactions

After ESWL, lumbodynia was of a shorter duration on an average in the medication group, and episodes of intermittent gross hematuria were less frequent on an average in this group. Lumbodynia had resolved within 3 days in 22 patients in the medication group, and in 14 patients in the control group. There was a significant difference between the two groups ($X^2 = 4.44$; $P < 0.05$). Lumbodynia had resolved within 1 week in 28 patients in the medication group, and in 21 patients in the control group. There was a

Table 3 Mean and standard deviations of plasma SOD ($\times 10^3$ U/L) and MDA (mmol/L) before and after ESWL (mean ± SD)

	Plasma SOD		Plasma MDA	
	Control ($n = 30$)	Medicated ($n = 30$)	Control ($n = 30$)	Medicated ($n = 30$)
Before	107.43 ± 16.89	108.91 ± 13.84	5.39 ± 2.26	5.93 ± 2.95
Post	102.06 ± 14.54	105.84 ± 23.25	6.37 ± 3.92	6.52 ± 3.19
ESWL24 h	98.21 ± 14.15	105.445 ± 22.66	7.77 ± 2.83[a]	6.43 ± 2.74[b]
ESWL72 h	88.83 ± 20.40[a]	103.85 ± 23.14[b]	9.47 ± 4.59[a]	7.67 ± 3.46[a, b]
ESWL7d	104.04 ± 17.98	112.54 ± 21.87[b]	7.02 ± 4.77	6.06 ± 3.62

[a] $P < 0.05$ indicates pre- versus post-ESWL

[b] $P < 0.05$ indicates control versus medicated

Table 4 Mean and standard deviations of the excretion of urine NAG (U/gCr), γ-GT (U/gCr) and β_2-MG (mg/gCr) before and after ESWL (mean ± SD)

	NAG		γ-GT		β_2-MG	
	Control (n = 30)	Medicated (n = 30)	Control (n = 30)	Medicated (n = 30)	Control (n = 30)	Medicated (n = 30)
Before	0.403 ± 0.21	0.395 ± 0.34	4.93 ± 2.26	3.81 ± 2.76	2.51 ± 1.70	2.48 ± 2.08
Post	0.45 ± 0.22	0.57 ± 0.51	7.21 ± 5.39	5.49 ± 5.01	4.33 ± 2.75[a]	3.83 ± 3.00[b]
ESWL24 h	0.70 ± 0.49[a]	0.46 ± 0.31[b]	9.99 ± 5.11[a]	4.28 ± 3.07[b]	3.36 ± 4.09	2.67 ± 2.77
ESWL72 h	0.60 ± 0.63[a]	0.415 ± 0.25	7.19 ± 4.14	4.79 ± 3.17[b]	3.11 ± 3.25	2.84 ± 3.38
ESWL7d	0.355 ± 0.13	0.29 ± 0.31	4.86 ± 2.99	3.62 ± 2.46	2.61 ± 2.70	2.32 ± 1.83

[a] $P < 0.05$ indicates pre- versus post-ESWL

[b] $P < 0.05$ indicates control versus medicated

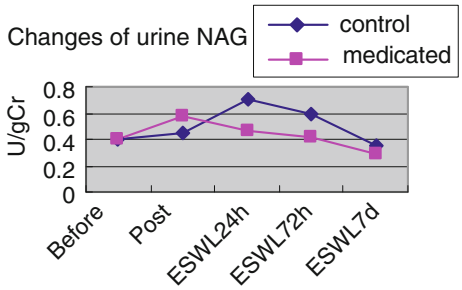

Fig. 6 Changes of urine NAG (U/gCr)

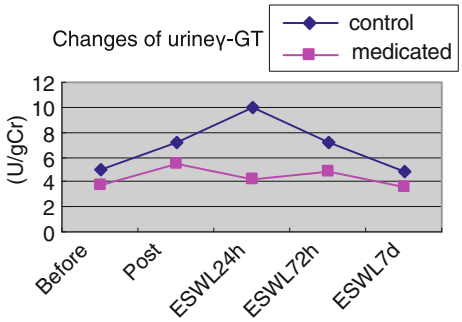

Fig. 7 Changes of urine γ-GT (U/gCr)

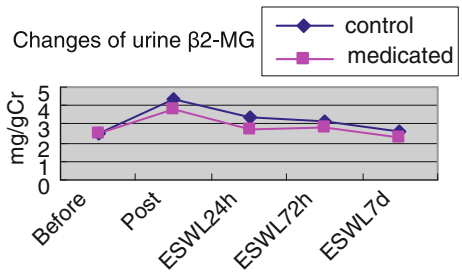

Fig. 8 Changes of urine β_2-MG (mg/gCr)

significant difference between the two groups ($X^2 = 5.45$; $P < 0.05$). Intermittent gross hematuria occurred less than three times in 27 patients after ESWL in the medication group, and in 20 patients in the control group. There was a significant difference between the two groups ($X^2 = 4.81$; $P < 0.05$). Intermittent gross hematuria occurred more than five times in 1 week after ESWL in two patients in the control group (Table 6).

Table 5 Compared with major effect at lithotripsy after ESWL

	Medicated (n = 30)		Control (n = 30)	
	First ESWL	Re-ESWL	First ESWL	Re-ESWL
Stone-free	15	2	10	5
Utility	10	3	8	5
Relief	4	2	7	4
Invalid	1	0	5	2

Adverse reactions of the medication

During the course of medication treatment there were no complaints of rash, nausea, vomiting, and anaphylactic shock. Five patients complained of frequent urination and a little torridness that was tolerable.

Discussion

Extracorporeal shock wave lithotripsy (ESWL) is a noninvasive, almost pain-free standard treatment modality for urolithiasis. However, ESWL is not completely free of side effects. After ESWL in our study groups, there was a significant increase in the excretion of β_2-microglobulin (β_2-MG), γ-glutamyltransferase (γ-GT), and *N*-acetyl-beta-D-glucosaminidase (NAG), which is consistent with numerous previous reports [2, 3, 11]. Because NAG, β_2-MG, and γ-GT are predominantly markers of the proximal tubule, an increase in these indices is representative of shock-induced impairment of proximal tubular protein reabsorption (β_2-microglobulin), and impairment of the cell membrane

Table 6 Compared with duration of lumbodynia and frequency of gross hematuria after ESWL

	Duration of lumbodynia				Frequency of gross hematuria			
	<1 day	1–3 days	4–7 day	>1 week	1	2–3	4–5	>5
Medicated ($n = 30$)	7	15	6	2	10	17	5	0
Control ($n = 30$)	4	10	7	9	7	13	8	2

integrity (NAG and γ-GT) [12]. Our study showed that post-ESWL urinary enzymes and β_2-MG in patients treated with the preparations were statistically lower than in the controls. Moreover, the content rate in the medication group was higher than in the controls ($P < 0.05$). Frequency of gross hematuria after ESWL was statistically lower, and duration of lumbodynia was significantly shorter than in the controls ($P < 0.05$).

Recently, numerous studies have shown that the energy released by shock waves produces cavitations or bubbles that may cause direct injury to the renal vasculature. Vascular injury causes ischemia in areas of tissue, which become susceptible to free-radical production as reperfusion occurs. Oxygen-free radicals might be an integral element in shock-wave-induced renal injury through an indirect mechanism. Free-radical formation and subsequent damage to the kidney may be attributable to shock wave lithotripsy in the same manner as in the ischemia-reperfusion model [1, 4, 6, 13].

It is well known that malondialdehyde (MDA) serves as a reliable marker of free-radical-mediated lipid peroxidation [14]. Superoxide dismutase (SOD) is the first line of defense against free-radical-mediated injury, and is an important indicator of anti-oxidation in vivo [15, 16]. Our results demonstrated significantly increased MDA levels and decreased SOD levels after ESWL in control patients. This is suggestive of free-radical-mediated lipid peroxidation of renal injury induced by ESWL. In this study, we have confirmed a strong protective effect of the traditional Chinese medications, as reflected by the significantly lower MDA and higher SOD values after ESWL in the medication group, as when compared with MDA and SOD in the control group.

Many herbs in the preparations had a strong anti-oxidant effect. Tang et al. [17] demonstrated that polysaccharides of common yam rhizome can increase serum SOD activity and consumption of catalase activity, decrease serum MDA, and strengthen the anti-oxidant effect. Tian et al. [18] demonstrated that fruit of medicinal cornel can scavenge free radicals, thus diminishing free-radical-mediated injury. Tian et al. [19] demonstrated that oleanolic acid, the main ingredient of plantaginis, may scavenge free radicals. In addition, Pian et al. [20] reported that common yam rhizome, fresh or dried root of Rehmannia, fruit of medicinal cornel, and Tuckahoe, may decrease serum MDA consumption, and improve local tissue SOD activity. There are many reports on the anti-oxidative effect of Astragalus membranaceus. Astragalus membranaceus could inhibit a pathologically increased influx of calcium ions, and thus it could prevent ischemia and subsequent free radical formation in a manner similar to that of the calcium channel blocker, verapamil. The main ingredients of Astragalus membranaceus, including polysaccharides, flavonoids and saponins, have a strong effect of clearing free radicals and increasing SOD activity [6]. Furthermore, Astragalus membranaceus is abundant in selenium, an important trace element, which is an essential component of glutathione peroxidase (GPX) [21]. GPX is responsible for the homeostasis of oxygen-derived free radicals, and protects the cell against oxidative membrane damage [22]. Selenium has been demonstrated to reduce shock-wave-induced cellular injury in cultured MDCK cells [23].

ET-1 was originally described as an endothelium-derived peptide with potent vasoconstrictor activity, involved in the pathogenesis of hypertension. Recent reports have demonstrated that the kidney is an important site for ET-1 synthesis and secretion, and that ET-1 plays a key role in the tubular function of the kidney in an autocrine/paracrine manner [24]. Some researchers have found that ET-1 levels increased after ESWL. The increased ET-1 levels might be related to cavitation (SWC) generated by shock waves, immediate endothelial cell injury and activation of RAAS (renin-angiotensin-aldosterone system) when ischemia occurred after ESWL [25, 26]. In our study, post-ESWL plasma ET-1 showed a significant increase in the control group, which was consistent with previous reports. Furthermore, we found that ET-1 levels were statistically higher than in the medication group ($P < 0.05$). This confirmed the protective effects of the preparation on endothelial cells. It has been reported that Astragalus membranaceus may enhance erythrocyte deformability, affect arachidonic acid metabolism, suppress thrombosis, and increase cAMP in platelets. Astragalus membranaceus, as a calcium antagonist, could inhibit the direct generation of ET-1 caused by pathologically increased influx of calcium ions after ESWL. Furthermore, Astragalus membranaceus might suppress the production of ET-1 by increasing the glomerular filtration rate and diminishing endothelial cell damage [27]. Many herbs in the preparation, including Lalang grass rhizome, Indian bread, Oriental water plantain

rhizome, Rehmannia dried rhizome, common yam rhizome, and tree peony bark, might improve renal blood flow and correct fibrinolytic hypersplenism, and thus decrease the production of vascular endothelin [28–30].

TNF-α is an important mediator of inflammation, and plays an important role in the organism's immune or inflammation response [31]. A few researchers have reported that TNF levels increase after ESWL. Our study confirmed this result, demonstrating that inflammation might participate in renal injury induced by ESWL. We found that the preparations could decrease the serum levels of TNF α after ESWL. It has been observed that Astragalus membranaceus can reduce TNF-α level in patients with chronic renal glomerular nephritis, and significantly reduce TNF-α level in domestic rabbit kidney injured by ischemia/reperfusion [32]. It has been reported that Rehmannia dried rhizome, common yam rhizome, and Fructus corni might reduce glomerular sclerosis by significantly decreasing TNF levels in patients. Indian bread could inhibit mesangial cell proliferation induced by TNF in patients [33].

NO, a highly reactive substance, is enzymatically generated by both constitutive nitric oxide synthase (cNOS) and inducible nitric oxide synthase (iNOS). NO production is regulated by various chemical stimuli, and by physical forces such as, shear stress, transmural pressure, and stretching of the vascular wall, which are continuously controlled by blood flow in vivo [34]. Wu et al. [35] reported that the major source of NO that causes vasodilatation is produced by cNOS during the early period of ischemia of renal parenchyma. Park et al. [36] reported that shock waves stimulate the NO-cyclic 3′,5′-guanosine monophosphate signaling pathway and increased mean plasma nitrite levels. They suggest that NO is released from renal endothelial cells, possibly by cyclic strain or pressure induced by SWL. Additionally, these investigators speculated that any NO produced may decrease renin production, preventing renal damage resulting from excessive renal vasoconstriction by the renin-angiotensin system. Aksoy et al. [37] also indicated an increase of plasma and urine NO levels in the acute period after SWL. The physiological role of endothelial-derived NO in regulating vasodilatation via vascular smooth muscle cells is well described. Clinical studies have indicated that increased levels of NO during ischemia of renal parenchyma may be protective enough for renal pathological alterations resulting from SWL-induced renal trauma. We found that plasma NO levels peaked by 24 h, which was consistent with these reports [38]. However, to our surprise, the second peak value of plasma was found 7 days after ESWL in our study. In other studies, it is suggested that reactive oxygen species (ROS) have a significant role in I/R injury after ESWL [2, 6, 37, 39]. Considerable lipopolysaccharide is produced during the later period of renal parenchymal injury, which is the important inducing factor of inducible nitric oxide synthase (iNOS). NO generated by iNOS in this period may be an important chemical modulator of inflammation, and can affect macrophage activity and the immune response [40]. In the study, plasma NO showed no significant increase in the medication group. Thus we speculate that the medications could modulate plasma NO levels after ESWL, which was the reason that Rehmannia dried rhizome and mountain cornus might cause the injured epithelial tissue to recover and inhibit the expression of iNOS in the kidney, thus reducing NO synthesis [18]. Astragalus membranaceus might reduce NO production by reducing the lipid peroxidation product in renal tubules and suppressing iNOS activity [41, 42].

Hematuria and low back pain are the most common complications after ESWL. In this study, lumbodynia was of a shorter duration on an average, and episodes of intermittent gross hematuria were less frequent in the medication group. This may be explained by the following four reasons: firstly, plantain herb, Oriental water plantain rhizome, and Spora lygodii promote the stone clearance by their obvious diuretic effectiveness. Reported by Yao [43], plantain herb can increase urea, uric acid, and sodium chloride excretion in dog, rabbit, and human models. Plantain herb and Oriental water plantain rhizome can inhibit the activity of the Na^+-K^+-ATP enzyme in the renal tubular epithelial cells. Oriental water plantain rhizome can inhibit Na^+ reabsorption by direct inhibition of K^+ secretion in the tubular collecting duct and increasing plasma atrial natriuretic peptic levels [43, 44]. In addition, Ou Yang et al. [45] showed that ureteral peristaltic frequency and ureteral intraluminal pressure increased significantly in dogs injected with Spora lygodii. Secondly, Christina loosestrife helps improve ureteral action potential, and has diuresis effectiveness since triterpene alcohol glycoconjugate (Ds–t), its main component, may increase urine volume in rats [46, 47]. Thirdly, Christina loosestrife and Spora lygodii can help promote excretion of Na^+, urea, uric acid, and Cl^- in renal tubular epithelial cells, and result in solute diuresis, which may relax ureter smooth muscle and strengthen ureter peristalsis [48]. Lastly, polysaccharides with being similar to acid mucopolysaccharide in structure, the main ingredients of lygodium and Indian bread can reduce the pH values of urine which may be available for dissolving of alkaline stones. Moreover, carboxyl, hydroxyl, carbonyl, amino and oxygen heterocycles of flavonoids, polysaccharides and organic acids, which are the main chemical ingredients of lygodium and Indian bread, can form soluble coordination compounds with Ca^{2+} ions in stones [49]. In addition, Lalang grass rhizome has the ability to reduce gross hematuria during ESWL [47].

In brief, the preparation of traditional Chinese medicines for invigorating the kidney and excreting calculus may be of significant benefit in protecting the kidneys against ESWL-induced morphological and functional injury. The preparations exert their effects by improving renal resistance to oxidative stress, ameliorating circulatory disorders, and interfering with local inflammation; however, further study is needed to evaluate the effects and potential usefulness of these Chinese traditional medicines with modern technology.

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