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ORIGINAL ARTICLE

Role of Removing Stasis and Reducing Heat Formula in Clearance of Proximal Ureteral Calculi after Ureteroscopic Ho:YAG Laser Lithotripsy: A Prospective Randomized Study

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Objective To prospectively evaluate the efficacy of Removing Stasis and Reducing Heat Formula in accelerating calculus clearance and improving lower urinary tract symptoms of patients with proximal ureteral calculi after ureteroscopic Ho:YAG laser lithotripsy.

Methods A total of 138 patients with proximal ureteral calculi underwent ureteroscopic Ho:YAG laser lithotripsy by a single endocrinologist. Stone size varied from 10 to 15 mm. After operation, the patients were randomly divided into three groups: the control group (group A), tamsulosin group (group B), and Removing Stasis and Reducing Heat Formula group (group C). The treatment lasted for 4 weeks or until stone clearance. The primary and secondary outcomes of the three groups at follow-up were assessed.

Results Of the 131 patients available for follow-up, 44 cases were in the group A, 45 in the group B, and 42 in the group C, respectively. The stone free rate at 2 weeks in the groups B and C were significantly higher than that in the group A (95.56%, 97.62% vs. 79.55%; all $P < 0.05$). The ureteral colic rate and mean time of fragment expulsion were significantly reduced in the groups B (4.44% and 7.86 ± 4.99 days) and C (2.43% and 6.76 ± 4.37 days) compared with the group A (22.73% and 11.54 ± 9.89 days, all $P < 0.05$). On the day of double-J ureteric stent removal, the group C differed significantly from the group A in the total International Prostate Symptom Score, irritative subscore, obstructive subscore, and quality of life score (all $P < 0.05$).

Conclusion Removing Stasis and Reducing Heat Formula in the medical expulsive therapy might be an effective modality for patients with calculus in the proximal uretera after ureteroscopic Ho:YAG laser lithotripsy.

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URINARY calculi mostly become symptomatic when the calculi migrate into the ureter to acute obstruction of the ureteral lumen. These stones have, depending on size and location, a high probability to pass spontaneously. If conservative treatments fail or have a low probability of success, stones have to be removed actively. For patients requiring stone (10-15 mm in size) removal, both shock-wave lithotripsy (SWL) and ureteroscopy are recommended firstline therapies.¹ Medical expulsion therapy has been used as an adjunctive method in patients with renal and/or ureteral calculi who had undergone SWL, and facilitated earlier spontaneous clearance of lower ureteral calculi as well as fragments.²⁻⁴ The large stones in the proximal uretera with potential serious outcomes such as decreased renal function require treatment. Chinese Herbal Formula (CHF) such as Clearing Heat and Promoting Diuresis Formula showed a tendency being superior to conservative treatments in medical expulsive therapy after SWL.⁵ In order to clarify the clinical value of Removing Stasis and Reducing Heat Formula, we designed the randomized prospective study to evaluate the efficacy of Removing Stasis and Reducing Heat Formula in promoting spontaneous passage of stone fragments and ameliorating lower urinary tract symptoms in patients with proximal ureteral calculi after ureteroscopic Ho:YAG laser lithotripsy (URL).

PATIENTS AND METHODS

Patients

A prospective randomized study was conducted at Shouguang Hospital of Traditional Chinese Medicine between June 2008 and June 2013. The study protocol was approved by the ethics committees at Shouguang Hospital of Traditional Chinese Medicine which is the cooperative hospital of Shandong University of Traditional Chinese Medicine. A written informed consent was obtained from each patient. A total of 138 patients with proximal ureteral calculi underwent URL were included in the study. All patients were diagnosed with proximal ureteral calculi based on plain-film radiographs of the kidney, ureter and bladder (KUB), urinary ultrasonography, intravenous urography, and retrograde pyelography. Noncontrast helical computed tomography was performed when necessary. Moreover, the patients underwent a series of measurements, including history, physical examination, complete blood cell count, blood electrolytes, and routine urinalysis as well as serum urea and creatinine.

Inclusion criteria

The patients with symptomatic stone, calculi being 10-15 mm in size and located in the proximal ureter (between the ureteropelvic junction and sacroiliac joint) and with moderate hydronephrosis were included. The presence and location of the stone were confirmed with ultrasonography and/or plain-film of KUB. The stone sizes were measured from the longest dimension in millimeters on plain-film.

Exclusion criteria

Exclusion criteria included fever, leukocytosis, the presence of ureteral stricture distal to the stone, the coexistence of a kidney stone on ultrasonography, and proximal stone migration during URL.

Surgical procedures

Patients were placed in the asymmetric lithotomy position. The stones were fragmented with both semirigid ureteroscopes (8 F/9.8 F, Richard Wolf GmbH, Knittlingen, Germany) and lithoclast (60 W, Coherent Medical Systems, CA, USA) under general or regional anesthesia. The laser produced an energy per pulse of 0.5 to 1 J with a pulse frequency of 5 to 10 Hz. After the placement of a safety guide wire, semirigid ureteroscope was inserted alongside the guide wire under direct vision without dilating the ureteral orifice. NTrap® (Cook Urological Inc., USA), a device to prevent the upward movement of stones during ureteroscopic lithotripsy, was inserted under direct vision via the ureteroscope. If the stones were embedded in the polypoid or edematous ureteral mucosa, lithotripsy was done to make a channel for NTrap to pass. Subsequently, the stones were fragmented to 2-3 mm sized particles by using a 550-μm holmium laser fiber so as to be spontaneously expelled. When ureteral calculi patients were complicated with polyps of ureter, polyps were resected with Ho:YAG laser. Finally, a double-J ureteric stent (5 F) was placed in the bladder.

All procedures were performed by an experienced surgeon. The operative time was recorded from the beginning of ureteroscope insertion through the urethra to withdrawal of the ureteroscope. The double-J ureteric stent was removed at 4 weeks after operation. Sixteen-French catheter was routinely placed and removed 1-3 days postoperatively.

Grouping and treatments

After operation, patients were randomly divided into three groups. The patients in the group A (placebo group) and C took Removing Stasis and Reducing Heat Formula. The

patients in the group B received tamsulosin 0.4 mg orally daily in the morning after breakfast for 4 weeks.

Removing Stasis and Reducing Heat Formula was composed of Dahuang (Radix et Rhizoma Rhei) 6 g, Taoren (Semen Persicae) 9 g, Chishao (Radix Paeoniae Rubra) 9 g, Chuanniuxi (Radix Achyranthis Bidentatae) 15 g, Jinqiancao (Herba Lysimachiae) 30 g, Huashi (Talcum) 9 g, Haijinsha (Spora Lygodii) 15 g, Wuyao (Radix Linderae) 9 g, Chuanlianzi (Fructus Toosendan) 9 g, and Gancao (Radix Glycyrrhizae) 9 g.

Decoctions were prepared by the Department of Pharmacy at the Shouguang Hospital of Traditional Chinese Medicine. The crude herbs were immersed in distilled water for 2 hours and decocted, filtered. The decoction was concentrated to 1 g/ml with a routine method and divided into two bags, and each bag contained 60 ml decoction herbs. Patients in the group C took one bag twice a day for 4 weeks or until stone clearance. The administered oral dose of the herb for the group A was 1/20 of the group C. The appearance and taste of decoctions administered to the group A and C were identical.

All patients underwent oral hydration with a total daily volume of 2000-3000 ml. When the stones were expelled, double-J ureteric stent was removed and hydration therapy was stopped. During the 4-week treatment period, diclofenac (75 mg) was given to relieve pain if necessary.

Follow-up

At each week follow-up visit, ultrasonography and plain-film of KUB were performed to confirm whether there were remaining fragments and location of residual fragments.

The primary outcomes were the stone free rate at 2, 4 weeks, occurrence of ureteric colic episodes during the 4-week period, and expulsion time. Stone expulsion was defined as the absence of any residual fragments or presence of a smaller than 3-mm clinically insignificant and asymptomatic residual calculus. An episode of flank pain, requiring emergency room visit, narcotic use, or inpatient admission was defined as a colicky episode. The expulsion time was defined as a period from random allocation to stone expulsion.

The secondary outcomes were total International Prostate Symptom Score (IPSS), irritative IPSS, obstructive IPSS, and quality of life score. Weak urinary stream, intermittent flow, straining to urinate, and incomplete emptying refer to obstructive symptoms. Frequency, urgency, and nocturia refer to irritative symptoms.

Statistical analysis

Statistical analysis was carried out using the commercial

software program Statistical Package for Social Sciences, version 19.0 (SPSS Inc., USA). Quantitative data were expressed as mean $\pm$ standard deviation (SD) and an unpaired *t* test was used for comparisons between groups. Categorical data were reported as count (percentage) and Chi-squared test was used to analyze the categorical data. *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Of the 138 randomized patients (46 in the group A, 48 in the group B, and 44 in the group C), the data of 2 patients from the group A, 3 from the group B, and 2 from the group C were not included in the final analysis for various reasons, including inability to fulfill timely follow-up (1, 2, and 1 cases, respectively), inadequate data for analysis (1 in the group A), postural hypotension associated with tamsulosin (1 case), and abdominal discomfort with Removing Stasis and Reducing Heat Formula (1 case). Demographic and clinical characteristics of the three groups were comparable (all $P > 0.05$, Table 1).

Primary outcomes

Two weeks postoperatively, the stone free rate were 79.55% (35/44), 95.56% (43/45), and 97.62% (41/42) in the groups A, B, and C respectively. The difference between the group A and the other two groups was statistically significant ($P = 0.022$ and 0.009 , respectively), but not significant at 4 weeks (all $P > 0.05$). The ureteral colic rate of the three group were 22.73% (10/44), 4.44% (2/45), and 2.43% (1/42) respectively, and difference between the group A and the other two groups was statistically significant ($P = 0.012$ and 0.005 , respectively). Although the mean time for fragment expulsion in the group B was slightly longer than that in the group C (7.86 ± 4.99 vs. 6.76 ± 4.37 days), the difference was not significant ($P = 0.280$). However, the expulsion time in the group B and C was significantly shorter than that in the A group (11.54 ± 9.89 days, $P = 0.032$ and 0.005 , respectively).

Secondary outcomes on the day of stent removal

There were significant differences between the group A and C ($P = 0.015$) and between the group B and C ($P = 0.031$) in the total IPSS score. The group C also differed significantly from the group A in the irritative subscore, obstructive subscore, and quality of life score ($P = 0.000$, 0.003 , and 0.012 , respectively). In the group B, only the obstructive score was differed significantly from the group A ($P = 0.021$). (Table 2)

Table 1. Demographic and clinical characteristics of the three studied groups[§]

Groups	n	Age (yrs)	Sex (n, male/female)	Stone size (mm)	Operative time (min)
A	44	39.73±11.01	29/15	12.43±1.46	42.55±5.68
B	45	42.56±12.33	33/12	12.78±1.20	43.47±6.77
C	42	40.71±10.75	28/14	13.45±1.50	44.19±6.83

§: Plus-minus values are means±SD.

Table 2. Comparisons of IPSS as well as quality of life score among the group A, B, and C[§]

Groups	Time	IPSS			QoL score
		Total score	Irritative subscore	Obstructive subscore	
A (n=44)	Preoperative	8.94±4.13	4.15±2.59	4.79±3.16	2.52±1.79
	On one day postoperatively	11.65±4.38	6.44±3.46	5.21±2.57	2.21±1.76
	On the day of stent removal	13.77±4.50*	7.48±3.50*	6.29±2.63* [#]	2.83±1.72*
B (n=45)	Preoperative	8.60±4.12	4.30±2.84	4.30±2.95	2.19±1.80
	On one day postoperatively	12.53±4.79	7.79±3.69	4.74±2.91	2.44±1.71
	On the day of stent removal	12.77±5.24*	8.05±3.88*	4.72±3.24	3.07±1.67*
C (n=42)	Preoperative	8.72±4.16	4.84±2.71	3.88±2.88	1.88±1.77
	On one day postoperatively	11.47±3.98	7.09±3.52	4.38±2.54	2.34±1.56
	On the day of stent removal	7.16±3.37	4.22±2.70	2.94±2.06	1.47±1.44

§: Plus-minus values are means±SD.

IPSS: International Prostate Symptom Score; QoL: quality of life.

*P<0.05 compared with the group C on the day of stent removal; [#]P<0.05 compared with the group A on the day of stent removal.

DISCUSSION

Stranguria with urinary stone or stranguria from urolithiasis,⁶ named as Lin or Lin Bi in Jin Gui Yao Lue, is characterized by dripping discharge of urine and difficulty and pain in micturition.⁷ Clearing heat, promoting diuresis, and tonifying kidney yang are the favorable principles to treat stones in the upper urinary tract, and have proved to be effective for the urinary stones less than 0.5 cm in transverse diameter. However, this therapeutic method does not achieve stone-discharging rate for those patients with transverse stone diameter more than 0.6 cm or stones staying immobile inside the kidney for years, as well as ones with lithic ureteral obstruction or hydronephrosis.⁶ The American Urological Association (AUA)/European Association of Urology (EAU) 2007 Guidelines recommended that for proximal ureteral stones >10 mm, ureteroscopic management yields significantly higher stone free rates.¹ Regardless of the modality used for fragmenting proximal ureteral calculi, the success of the procedure depends on the passage of stone fragments. Untreated residual fragments may serve as a source of recurrent stone growth,

persistent infection, and ureteric colic, further increasing morbidity and costs.⁸

Blood stasis is clinically manifested by pains, fever, skin and mucosa abnormality, stagnation, lumps and hemorrhage.⁹ During URL, laser energy would result in ureteral mucosal edema, trauma, and hemorrhage. The passage of stone fragments and ureteral stenting are related with many potentially uncomfortable urinary symptoms or morbidity such as flank or suprapubic pain, urinary frequency/urgency, dysuria, hematuria, urinary tract infection or fever, and other voiding symptoms, which cause a significant decrease in patient health-related quality of life.¹⁰⁻¹² Therefore, blood stasis and heat-damp may coexist in the post-URL patients.

According to Liu Youfang's experience in treatment of urolithiasis with Traditional Chinese Medicine,⁶ we designed the Removing Stasis and Reducing Heat Formula to remove blood stasis and reduce heat-damp, promote qi-circulation and relieve diuresis, relieve pain and arresting the bleeding for urinary stone patients post-URL. Dahuang and Taoren are the main ingredients to relieve stasis and heat. Dahuang helps remove stagnation by purgation, activate blood circulation and remove blood

stasis, clear and purge damp-heat;^{13, 14} Taoren can promote blood circulation to resolve stasis.¹⁵ Of the five minister ingredients, Chishao has the effects of clearing heat, cooling blood, activating blood, and resolving stasis, which can stop bleeding without causing blood stasis and activate blood without causing bleeding; Chuanniuxi can promote blood circulation, which is combined with Chishao to assist monarch ingredients to remove blood stasis, stop bleeding, and promote qi-circulation; both Jinqiancao¹⁶ and Huashi are utilized to promote diuresis; Haijinsha is effective on relieving pain of the urethra. Assistant ingredients, Wuyao and Chuanlianzi, promote qi flow to relieve pain. Gancao can relieve spasm and pain and harmonize all ingredients, serving as the guide ingredient.

In the prospective randomized study, we compared the efficacy of the group A, B, and C in clearance of calculi in the proximal ureters after URL in the clinical setting. Our results showed both CHF and tamsulosin significantly promoted stone expulsion, reduced occurrence of colic episodes, and decreased expulsion time. However, the CHF was more effective in terms of total IPSS, irritative subscore, obstructive subscore, and quality of life score. According to the therapeutic indication of URL for urinary stone, URL should be firstly carried out to eliminate the acute symptoms; then CHF was administrated to remove blood stasis and reduce heat-damp, promote qi-circulation and diuresis, and relieve pain and stop bleeding.

The results of this study suggest Removing Stasis and Reducing Heat Formula in the medical expulsive therapy might be an effective modality for patients with calculus in the proximal ureters after URL. In the future, large-scale, prospective, and randomized study will be needed.

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