EFFECTS OF MINIMALLY INVASIVE SURGERY COMBINED WITH METHYLPREDNISOLONE AND TAMSULOSIN ON THE PROGNOSIS OF CALCIUM-CONTAINING URETERAL CALCULI AND THE LEVELS OF URINARY MONOCYTE CHEMOTACTIC PROTEIN-1, TREFOIL FACTOR 1, AND HIGH-MOBILITY GROUP BOX PROTEIN 1

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ABSTRACT

Introduction*: Although extracorporeal shock wave lithotripsy (ESWL) is the preferred treatment for ureteral calculi, the subsequent non-discharge of stones leads to poor prognosis. This study aimed to investigate the clinical outcome of ESWL combined with tamsulosin and/or methylprednisolone.*

Materials and methods*: From June 2013 to June 2016, 180 patients with calcium-containing ureteral calculi were treated with ESWL and equally randomized into three groups: group A, control patients; group B, patients treated with tamsulosin; and group C, patients treated with tamsulosin and methylprednisolone. The endpoints were stone excretion and adverse reactions. Further, the levels of urinary calcium, monocyte chemotactic protein-1 (MCP-1), trefoil factor 1 (TFF1), and high-mobility group box protein 1 (HMGB1) were determined before and after treatment.*

Results*: The stone excretion rate was higher in groups B and C than in group A. The stone discharge time, renal colic frequency, analgesic use frequency, stone street formation rate, and repetitive treatment rate were lower in group C than in group B, and lower in groups B and C than in group A (P<0.05). No drug-related toxicities were recorded. Urinary calcium and HMGB1 levels were lower after treatment, whereas the TFF1 level showed a higher increase in group A than in groups B and C. The changes in group C were more significant than those in group B (P<0.05). There was no significant difference in pre-and postoperative MCP-1 levels among the three groups.*

Conclusions*: The combination of methylprednisolone and tamsulosin along with ESWL in the treatment of calcium-containing ureteral calculi has a high efficacy and can improve the level of urinary inflammatory factors with a good safety outcome.*

Keywords: *Minimally invasive surgery, methylprednisolone, tamsulosin, calcium-containing ureteral calculi, prognosis, monocyte chemoattractant protein.*

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Introduction

Calcium-containing ureteral calculi, including calcium oxalate stones and infectious stones, account for >80% of urinary stones, and their formation has been associated with excessive urinary salt level, decreased activity of inhibitors, and renal epithelial cell membrane surface damage[1]. Extracorporeal shock wave lithotripsy (ESWL) is the preferred treatment for ureteral calculi with a diameter of >5 mm. The advantages of ESWL, including minimal invasiveness, rapid recovery, and low cost, are widely recognized. However, the excretory process is often accompanied by renal colic, lower urinary tract symptoms, and even the formation of a stone street because of non-discharge of stones, affecting the prognosis of patients and increasing their pain and economic burden[2]. Recently, α1-blockers and glucocorticoids have been widely used in the treatment of ureteral calculi and are considered to significantly accelerate stone excretion and improve the spontaneous stone excretion rate[3].

Concomitantly, a large number of studies have shown that cell injury and the inflammatory response may be important factors in the formation of renal calculi in hypercalciuria[3-7]. Therefore, detection of postoperative urinary inflammatory factors, including changes in monocyte chemotactic protein-1 (MCP-1), trefoil factor 1 (TFF1), and high-mobility group box protein 1 (HMGB1) levels, is important for the comprehensive assessment of patient prognosis[4]. In this study, 180 patients treated at Jilin Province People's Hospital of Changchun were included. The safety and effect of ESWL combined with α1-blockers and glucocorticoids on urinary inflammatory factors were analyzed in a prospective manner.

Materials and methods

General data

A total of 180 patients with calcium-containing ureteral calculi (≤10 mm) admitted to our hospital between June 2013 and June 2016 were divided into groups A, B, and C according to the random number table method. There were no significant differences in baseline age, body mass index, stone diameter, calculus composition, and 24-h urinary calcium level among the three groups (P>0.05) (Table 1). The study was approved by our hospital medical ethics committee (registration number 2016J020) and written informed consent was obtained from the patients and their families.

Indexes		Group A (n=60)	Group B (n=60)	Group C (n=60)	P	P
Age (y)		42.58±10.17	43.03±10.18	42.72±10.04	0.97	>0.05
Body mass index (kg/m^2)		22.77±3.24	22.92±3.29	22.71±3.17	0.94	>0.05
Stone diameter (mm)		11.56±3.16	11.48±3.10	11.63±3.05	0.96	>0.05
Sex	Male	33 (55.00)	31 (51.67)	35 (58.33)	0.76	>0.05
	Female	27 (45.00)	29 (48.33)	25 (41.67)		
Calculus composition	Calcium oxalate	48 (80.00)	46 (76.67)	47 (78.33)	0.91	>0.05
	Calcium phosphate	12 (20.00)	14 (23.33)	13 (21.67)		
Stone location	Upper ureter	39 (65.00)	35 (58.33)	37 (61.67)	0.75	>0.05
	Middle and lower ureter	21 (35.00)	25 (41.67)	23 (38.33)		
Side of stone	Left	28 (46.67)	31 (51.67)	29 (48.33)	0.87	>0.05
	Right	32 (53.33)	29 (48.33)	31 (51.67)		

Table 1: Comparison of baseline clinical data among the three groups, n (%).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) ureteral stones confirmed on radiography and calcium oxalate or calcium phosphate composition of stones detected using infrared spectroscopy[4], (2) solitary stone and negative urinary bacterial culture, and (3) no history of drug use affecting stone excretion within 2 weeks before enrollment.

The exclusion criteria were as follows: (1) no stone detected on radiography; (2) gross hematuria, pyuria, or positive urinary bacterial culture; (3) combined urinary tract infection, ureteral stricture, and liver and kidney dysfunction; (4) history of urinary surgery 6 months before enrollment; and (5) history of allergies to α1-receptor blockers and glucocorticoids or other contraindications.

Research methods

Treatment regimens

A total of 180 patients underwent ESWL using the Dornier Compact lithotripter (Dornier Medical Systems, Weßling, Germany). Lithotripsy was performed under radiographic monitoring, with a seismic frequency of 80 times/min and shock wave energy of 6-8 kV. Treatment was considered complete when the shock wave number reached 3000 or satisfactory stone crushing (changes in stone size or shape or gravel stone fragments) was achieved[5]. Oral pills for urinary stones were administered postoperatively (Dongguan Asia Pharmaceutical Co., Ltd., Guangdong, China; 4 g per pill, 2 times a day).

Based on the above regimen, group A patients were not treated with other drugs. Group B patients were orally administered with 0.2 mg tamsulosin (once a day [qd]) sustained-release capsules (Astellas Pharmaceutical Co., Ltd., Halle, Germany; 0.2 mg per capsule) at night. Group C patients were treated with tamsulosin (QD) sustained-release capsules and methylprednisolone (2 mg, qd). The dosage of tamsulosin in group C was similar to that in group B. Methylprednisolone (Medrol; Pfizer Italia S.r.l.; 4 mg per tablet) was administered orally, once daily at 2 mg/kg. The time of administration was the day after ESWL. The withdrawal time was after stone excretion or 4 weeks postoperatively for tamsulosin and after stone excretion for methylprednisolone. The medication duration was ≥10 days[6].

Follow-up program

Patients were followed up for a period of 3 months or until the stones were cleared or other treatments were needed. In the first month, physical examination, urinary B-ultrasound, and KUB (kidney, ureter, bladder) examination were conducted once a week, followed by physical examination, urinary B-ultrasound, and KUB examination every month until stone excretion or conversion to other treatment options. The follow-up methods mainly consisted of outpatient follow-up examinations, follow-up questionnaire survey, and telephone follow-up or home visits, if necessary.

Outcome measures

Efficacy observation: The main observation outcomes of stone discharge included stone excretion rate, stone discharge time, stone removal rate, renal colic frequency, analgesic use frequency, stone street formation rate, repeated ESWL treatment, or conversion to other treatment options. The stone excretion rate refers to the stone composition ratio after a single ESWL procedure, and the stone removal rate indicates the stone composition ratio from a single ESWL procedure until the end of follow-up[7]. Analgesic use refers to intramuscular injection of tramadol, bucinnazine, pethidine, and other strong analgesic drugs.

Safety evaluation: All expected and unexpected adverse effects of the administered drugs and the degree of symptoms, frequency of occurrence, duration, and treatment measures were recorded, and the causes were analyzed.

Urine test: Urine was collected at early morning for urine calcium level measurement (Arsenazo method). The kit was purchased from Jinan Baibo Biotechnology Co., Ltd. (enzyme-linked immunosorbent assay). Midstream urine was used for MCP-1, TFF1, and HMGB1 detection[8]. The kit was purchased from Shanghai Yinggong Biotech Co., Ltd. A micropore coated with MCP-1/TFF1/HMGB1 antibody was incubated and thoroughly washed with samples, standard products, and horseradish peroxidase-labeled antibodies. The color of 3,3,5,5-tetramethylbenzidine, as a substrate, changed to blue upon catalysis of peroxidase and finally to yellow upon the action of an acid. There was a positive correlation between color and MCP-1/TFF1/HMGB1 in the samples. Absorption was determined with an enzyme marker at a 450-nm wavelength.

Survival analysis: The cumulative survival rates were analyzed using the survival curve method.

Statistical analysis

All data for this clinical study were analyzed using SPSS 18.0. Count data are expressed as number (percentage). The χ^2 test was used for measurement of means and standard deviations ($\bar{x}\pm s$). An independent-sample t-test was used for data with normal distribution and variance homogeneity. If the variance was not homogeneous, the correction t-test was used. Data with non-normal distribution are presented as M (Q1, Q3) and analyzed using the Wilcoxon rank sum test. A P-value of <0.05 was considered statistically significant.

Results

Efficacy observation

The stone excretion and removal rates were higher in groups B and C than in group A. Moreover, the stone discharge time, renal colic frequency, analgesic use frequency, stone street formation rate, and repetitive treatment rate were lower in groups B and C than in group A (P<0.05). The stone removal rate, renal colic frequency, analgesic use frequency, and repeated treatment rate in group C were lower than those in group B (P<0.05) (Table 2).

Indexes	Group A (n=60)	Group B (n=60)	Group C (n=60)	P	P
Excretion rate of stone, n (%)	46 (76.67)	56 (93.33)*	56 (93.33)#	0.01*#	<0.05
Time of stone excretion (d), $\bar{x}\pm s$	3.43±0.91	2.17±0.69*	1.38±0.58#&	0.00*#&	<0.05
Stone removal rate, n (%)	51 (85)	39 (65)*	26 (43.33)#&	0.01* 0.00# 0.02&	<0.05
Number of renal colic (times), $\bar{x}\pm s$	0.38±0.49	0.18±0.39*	0.08±0.28#&	0.04* 0.00# 0.29&	<0.05 <0.05 >0.05
Times of analgesic use, n (%)	36 (60.00)	22 (36.67)*	11 (18.33)#&	0.01* 0.00# 0.03&	<0.05
Stone street formation rate, n (%)	6 (11.67)	1 (1.67)*	1 (1.67)#	0.02*#	<0.05
Repetitive treatment rate, n (%)	24 (40)	13 (21.67)*	5 (8.33)#&	0.03# 0.00* 0.04&	<0.05

Table 2: Comparison of therapeutic effects among the three groups of patients.
*Note: *Comparison of group B and group A. #Comparison of group C and group A. &Comparison of group C and group B.*

Safety observation

There were no drug-related toxicities in group A, whereas slight dizziness, nausea, and other symptoms were found in groups B and C, all of which spontaneously resolved. No special treatment was provided.

Urine test

The urinary calcium and HMGB1 levels in the three groups were lower than the preoperative values. Moreover, the TFF1 level in group A showed a significantly greater increase than that in groups B and C. The changes in group C were more significant than those in group B, and the difference was statistically significant (P<0.05). There was no significant difference in the preoperative and postoperative MCP-1 levels among the three groups (P>0.05) (Table 3).

The survival curve showed that the cumulative survival rate was the highest in group A followed by group B, whereas the cumulative survival rate was the lowest in group C (Figure 1).

Discussion

ESWL has the advantages of a shorter excretion time and lower complication rate than conservative treatment. ESWL has minimal invasiveness

compared with gravel and stone removal and open ureteroscopy surgery, as well as a high success rate(9). Therefore, ESWL has been the preferred minimally invasive treatment for ureteral calculi. However, the process of stone excretion is still needed after ESWL. During this period, the stone discharge process is associated with ureteral irritation and may lead to ureteral smooth muscle spasms, mucosal edema, infections, renal colic, retained stones in severe cases, or even hydronephrosis[10,11]. It is important to effectively reduce ureteral smooth muscle spasms and mucosal edema during this period to improve patient prognosis.

Indices	Period	Group A (n=60)	Group B (n=60)	Group C (n=60)	P	P
Urinary calcium (mg/24 h)	Before surgery	204.37±68.49	199.39±79.19*	200.13±65.35#&	0.62* 0.67# 0.94&	>0.05
	After surgery	161.92±41.49	133.47±41.49*	134.06±27.27#&	0.00* 0.00# 0.96&	<0.05 <0.05 >0.05
	Pθ	0.00; <0.05	0.00; <0.05	0.00; <0.05		
MCP-1 (pg/mL)	Before surgery	142.39±21.05	139.35±23.28*	142.62±17.76#&	0.40* 0.95# 0.36&	>0.05 >0.05
	After surgery	140.52±20.70	138.25±20.20*	137.92±13.69#&	0.53* 0.47# 0.92&	>0.05 >0.05
	Pθ	0.60; >0.05	0.76; >0.05	0.19; >0.05		
TFF1 (ng/mL)	Before surgery	20.60±3.52	21.11±3.49*	20.88±3.90#&	0.40* 0.64# 0.70&	>0.05
	After surgery	22.03±2.71	23.98±3.12*	25.67±3.08#&	0.00* 0.00# 0.00&	<0.05 <0.05 <0.05
	Pθ	0.020; <0.05	0.00; <0.05	0.00; <0.05		
HMGB1 (pg/mL)	Before surgery	3091.12±960.80	3061.53±780.18*	3186.53±795.56#&	0.74* 0.18# 0.32&	>0.05
	After surgery	2641.85±552.57	2035.75±534.66*	1705.05±251.06#&	0.00* 0.00# 0.01&	<0.05 <0.05 <0.05
	Pθ	0.00; <0.05	0.00; <0.05	0.00; <0.05		

Table 3: Comparison of urinary calcium and urinary inflammatory factors before and after treatment in the three groups ($\bar{x}$±s).

*Note: *Comparison of group B and group A. #Comparison of group C and group A. &Comparison of group B and group C. θComparison with preoperative values.*

MCP-1, monocyte chemotactic protein-1; TFF1, trefoil factor 1; HMGB1, high-mobility group box protein 1

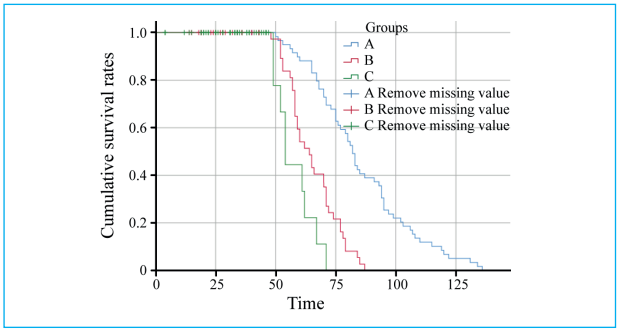

Figure 1: Results of the analysis of the cumulative survival rate.

In traditional Chinese medicine, pills for urinary stones are commonly used as auxiliary drugs after ESWL. The main adverse effects of these drugs for stone removal include heat, dampness, and blood stasis; however, the specific pharmacological mechanisms are unclear[12]. The results of the present study showed that the stone excretion and removal rates were not ideal only in group A (administered with oral pills for urinary stone only), indicating that simple application of auxiliary drugs for stone excretion had limited efficacy.

As a high-selectivity α-adrenergic receptor blocker, tamsulosin selectively blocks ureteral smooth muscle α1 and α1D receptors, thereby reducing the frequency and amplitude of ureteral smooth muscle peristalsis and consequently reducing ureteral smooth muscle spasm and controlling ureteral wall tension. In addition, as tamsulosin does not affect the natural peristalsis of the ureter, it also does not affect the postoperative ureteral pressure and urine transmission power[13]. Lopes et al.[14] found that tamsulosin can increase the pulse of urine flow and lower the ureteral lumen pressure, thus creating a pressure gradient below the stone that can aid early and complete stone discharge. In this study, the stone excretion rate, stone removal rate, and stone discharge time were better in group B than in group A, which confirmed the above conclusions. In addition, tamsulosin has a positive effect on the relaxation of the bladder neck and prostatic urethra[15]. Thus, it can reduce postoperative pain, stone street formation, and other serious complications and further improve the prognosis.

It should be noted that despite the positive role of tamsulosin in the expansion of the ureter and promotion of stone discharge, it cannot provide adequate relief of ureteral mucosal edema, which is considered to be another important factor in stone discharge[16]. At the same time, as a condition that is closely related to the inflammatory reaction, persistent edema of the ureteral mucosa in patients with calcium-containing ureteral calculi is often associated with increased prostaglandin synthesis, increased renal blood flow, and ureteral stenosis progression. Furthermore, ESWL-induced local ureteral trauma may exacerbate the pathophysiological changes and subsequently lead to postoperative renal colic, stone excretion difficulties, and even stone street formation[17]. Methylprednisolone, as a representative glucocorticoid, can interrupt the above-mentioned adverse cycle, inhibiting prostaglandin synthesis in vivo. Thus, patients in group C achieved a more ideal stone discharge rate. Moreover, as benefits of the short course of treatment and the small dose of methylprednisolone, patients in group C had no drug-related serious adverse events, confirming the safety of this regimen.

In the observation of urinary inflammatory factors, we found that the different treatment options had a different impact on urinary TFF1 and HMGB1 levels, in which the treatment regimen of ESWL combined with methylprednisolone and tamsulosin had the most ideal effect with respect to improving urinary inflammatory factors. Moreover, the increase in TFF1 level can inhibit the growth and aggregation of calcium oxalate crystals. The decrease in HMGB1 level indicated that renal tubular epithelial basement membrane injury was alleviated and renal interstitial supersaturated crystal deposition was reduced[18]. These results suggested that patients receiving this combination therapy may have a lower risk of postoperative recurrence of calcium-containing ureteral calculi and renal function involvement. Nevertheless, the effect of the regimen on the long-term prognosis of patients requires further studies with a large sample and long-term follow-up.

Conclusion

ESWL combined with methylprednisolone and tamsulosin for the treatment of calcium-containing ureteral stones had high efficacy and good safety for patients, with significant effects in the improvement of urinary calcium, TFF1, and HMGB1 levels. This treatment is expected to promote further improvement in the prognosis of patients, although its specific mechanism and long-term efficacy need to be further investigated.

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