

# Efficacy of Phloroglucinol Tamsulosin Combination Therapy for Medical Expulsion of Lower Ureteral Calculi and Influence on Patients' Cys-C Level

Yutong Li, Bin Pan, Guo Chen, Ying Wu\*

The First Affiliated Hospital of Jinan University, Guangzhou, China

## Email address:

liyutong@jnu.edu.cn (Yutong Li), panbin@jnu.edu.cn (Bin Pan), cgapple@21cn.com (Guo Chen), wuying20050511@126.com (Ying Wu)

\*Corresponding author

## To cite this article:

Yutong Li, Bin Pan, Guo Chen, Ying Wu. Efficacy of Phloroglucinol Tamsulosin Combination Therapy for Medical Expulsion of Lower Ureteral Calculi and Influence on Patients' Cys-C Level. *American Journal of Clinical and Experimental Medicine*.

Vol. 9, No. 1, 2021, pp. 17-21. doi: 10.11648/j.ajcem.20210901.14

Received: February 2, 2021; Accepted: February 12, 2021; Published: March 30, 2021

**Abstract:** Objective: Phloroglucinol is a myotropic, non-atropine and non-papaverine smooth muscle antispasmodic which directly acts on the smooth muscles of the gastrointestinal tract and the urogenital tract with no anticholinergic effect, no symptoms like xerostomia, visual impairment, dysuria, hypotension, increased heart rate, and arrhythmia etc. To investigate the efficacy of phloroglucinol tamsulosin combination therapy for medical expulsion of lower ureteral calculi and influence on patients' Cys-C level. Methods: Equally randomized 136 patients with lower ureteral calculi in our hospital into mono therapy group (phloroglucinol alone) and combination therapy group (additional tamsulosin was advised). The expulsion rate, expulsion time, stone diameter and levels of IL-10, CRP, NGAL, Cys-C, KIM-1 were compared between two groups, also with the effectiveness and the rate of adverse reactions. Results: The combination therapy group showed higher expulsion rate ( $P<0.05$ ) and shorter expulsion time ( $P<0.05$ ) than that of the mono therapy group and the stone diameter was slightly larger as well ( $P<0.05$ ). Also, patients under combination treatment had elevated IL-10, CRP, NGAL, Cys-C and KIM-1 levels and a better overall response rate ( $P<0.05$ ) while it was associated with a slightly higher rate of adverse reactions ( $P>0.05$ ). Conclusions: Phloroglucinol tamsulosin combination therapy had clear advantages on medical expulsion of lower ureteral calculi in respect of higher expulsion rate and elevated IL-10, CRP, NGAL, Cys-C and KIM-1 levels with larger stone diameter in a shorter time.

**Keywords:** Phloroglucinol Injection, Tamsulosin, Lower Ureteral Calculi

## 1. Background

The symptoms of ureteral stones and kidney stones are basically identical but primary ureteral stones are relatively rare which are mostly caused by kidney stones stuck in a narrow part of the ureter during expulsion [1, 2]. There are three types of ureteral calculi: upper, middle and lower [3]. Phloroglucinol is a myotropic, non-atropine and non-papaverine smooth muscle antispasmodic which directly acts on the smooth muscles of the gastrointestinal tract and the urogenital tract with no anticholinergic effect, no symptoms like xerostomia, visual impairment, dysuria, hypotension, increased heart rate, and arrhythmia etc. associated, and no effect on cardiovascular function compared with other smooth muscle antispasmodics [4]. Tamsulosin is usually used for the

treatment of Benign Prostate Hyperplasia (BPH) to block the  $\alpha_1A$  adrenergic receptors in the prostate through selective  $\alpha_1$  blockers and relax the smooth muscle of the prostate, thereby relieving related urinary system symptoms [5-8]. This article aims to investigate the efficacy of phloroglucinol tamsulosin combination therapy for medical expulsion of lower ureteral calculi and influence on patients' Cys-C level.

## 2. Data and Methods

### 2.1. Data

Clinical data were collected from 136 patients with lower

ureteral calculi in our hospital (from December 2018 to January 2020) who had been equally randomized into mono therapy group (phloroglucinol alone) and combination therapy group (additional tamsulosin was advised), each for 68. 39 males and 29 females aged 43~66 (mean age  $53.1 \pm 8.5$ ) with stones 10~20mm in diameter (average  $15.1 \pm 1.6$ mm) were enrolled in the mono therapy group. 35 males and 33 females aged 41~65 (mean age  $53.1 \pm 7.5$ ) with stones 10~18mm in diameter (average  $15.3 \pm 2.6$ mm) were enrolled in the combination group. Two groups were comparable in general condition with no statistical significance.

Inclusion criteria: patients who were diagnosed with lower ureteral stones (10~20mm in diameter) by abdominal ultrasound, plain film and other imaging examinations.

Exclusion criteria: patients with incomplete medical records; patients with exacerbation; patients with mental disorders and unable to cooperate; patients with major illness in heart and brain etc.

All patients and their families were informed about this study and signed an informed consent form.

## 2.2. Methods

### 2.2.1. Treatment

Both groups were given drotaverine hydrochloride tablets for conventional treatment. The mono therapy group was given diluted phloroglucinol IV drip (40mg/time, 3 times/d). The combination group was given additional tamsulosin capsules (2 capsules/time, 1 time/d) on the premise of the phloroglucinol treatment. Both took 4 weeks as a course of treatment with a total of 3 courses.

Overall response rate = significantly effective rate + effective rate.

## 2.3. Statistical Methods

Data were analyzed by SPSS21.0. The measurement data was indicated by ( $\bar{x} \pm s$ ), with t-test on independent sample among groups; the enumeration data was indicated by % with chi-square test.  $P < 0.05$  was considered statistically significant.

**Table 1.** Expulsion rate, expulsion time and stone diameter in two groups ( $\bar{x} \pm s$ ).

Group	Case (n)	Expulsion rate (n/%)	Expulsion time (d)	Stone diameter (mm)
Combination therapy	68	60 (88.23)	$4.74 \pm 1.16$	$4.85 \pm 1.30$
Mono therapy	68	51 (75)	$7.84 \pm 2.22$	$4.37 \pm 1.12$
<i>t</i>		4.340	9.582	0.220
<i>P</i>		0.036	0.001	0.030

## 3. Results

### 3.1. Comparisons of the Expulsion Rate, Expulsion Time and Stone Diameter

As shown in Table 1, the expulsion rate of the combination therapy group was 88.23% which was significantly higher than that of the mono therapy group (75%), also with a shorter expulsion time and slightly larger stone diameter, all indicating statistical significance ( $P < 0.05$ ).

### 2.2.2. Comparisons of the Expulsion Rate, Expulsion Time and Stone Diameter

Used KUB to measure the expulsion rate, expulsion time and stone diameter in two groups.

### 2.2.3. Comparisons of the IL-10 and CRP Levels Before and After Treatment

Used Immunoturbidimetric method to determine the IL-10 and CRP levels: prepared 3 test tubes and labeled them as a standard tube, a measuring tube and a blank tube. Added 350μL buffer to all 3 test tubes with additional 20μL ALT and AST standard to the standard tube, 20μL serum to the test tube, and 20μL of distilled water to the blank tube, then shook them respectively. After standing at room temperature for 5-10 minutes, conducted colorimetric assay with a spectrophotometer. Zero set the blank tube at a wavelength of 500nm and recorded the absorbance then analyzed the IL-10 and CRP levels with reference to that.

### 2.2.4. Comparisons of the NGAL, Cys-C and KIM-1 Levels Before and After Treatment

Used enzyme-linked immunosorbent assay to analyse the NGAL, Cys-C and KIM-1 levels.

### 2.2.5. Determination of the Overall Response Rate

The treatment effect was divided into three standards: significantly effective, effective and ineffective. Significantly effective: patients' clinical symptoms disappeared, including waist pain, hematuria, and edema etc. Effective: patients' clinical symptoms were significantly improved, including waist pain, hematuria, and edema etc. Ineffective: the clinical symptoms were not improved or even aggravated, and failed to remove the stones.

### 3.2. Comparisons of the IL-10 and CRP Levels Before and After Treatment

As shown in Table 2, the levels of IL-10 and CRP in two groups before treatment were not statistically significant ( $P > 0.05$ ) while the levels both elevated after treatment, with the combination therapy group higher than that of the mono therapy group, indicating statistical significance ( $P < 0.05$ ).

**Table 2.** IL-10 and CRP levels before and after treatment ( $\bar{x} \pm s$ ).

Group	IL-10 ( $\mu\text{g/mL}$ )		CRP ( $\text{mg/L}$ )	
	before	after	before	after
Combination therapy	6.27 $\pm$ 1.22	7.94 $\pm$ 1.67	5.11 $\pm$ 1.24	6.34 $\pm$ 1.57
Mono therapy	6.46 $\pm$ 1.21	6.82 $\pm$ 1.25	5.22 $\pm$ 1.16	5.57 $\pm$ 1.10
<i>t</i>	0.826	4.126	0.532	3.081
<i>P</i>	0.375	0.001	0.566	0.002

### 3.3. Comparisons of the NGAL, Cys-C and KIM-1 Levels Before and After Treatment

As shown in Table 3, the levels of NGAL, Cys-C and KIM-1 in two groups before treatment were not statistically significant ( $P>0.05$ ) while the levels both elevated after treatment with the combination therapy group higher than that of the mono therapy group, indicating statistical significance ( $P<0.05$ ).

**Table 3.** NGAL, Cys-C and KIM-1 levels before and after treatment ( $\bar{x} \pm s$ ).

Group	NGAL ( $\mu\text{g/L}$ )		Cys-C ( $\mu\text{g/L}$ )		KIM-1 ( $\text{ng/L}$ )	
	before	after	before	after	before	after
Combination therapy	3.50 $\pm$ 0.66	4.43 $\pm$ 0.72	518.12 $\pm$ 122.82	778.42 $\pm$ 86.30	72.22 $\pm$ 7.62	87.73 $\pm$ 11.12
Mono therapy	3.49 $\pm$ 0.60	4.04 $\pm$ 0.74	503.42 $\pm$ 62.26	678.32 $\pm$ 79.26	75.16 $\pm$ 8.86	76.35 $\pm$ 10.25
<i>t</i>	0.836	2.868	0.787	6.426	0.605	5.732
<i>P</i>	0.912	0.003	0.414	0.001	0.532	0.001

### 3.4. Comparisons of the Overall Response Rate

As shown in Table 4, the overall response rate in the combination therapy group was significantly higher than that of the mono therapy group, indicating statistical significance ( $P<0.05$ ).

**Table 4.** Overall response rate in two groups [*n*, (%)].

Group	Case (n)	Significantly effective	effective	ineffective	Overall response rate
Combination therapy	68	36	26	6	62 (91.17)
Mono therapy	68	26	25	17	51 (75.00)
$\chi^2$					4.46
<i>P</i>					0.03

### 3.5. Comparisons of the Incidence of Adverse Reactions

As shown in Table 5, the incidence of adverse reactions in the combination therapy group was higher than that of the mono therapy group.

**Table 5.** Incidence of adverse reactions in two groups [*n*, (%)].

Group	Case (n)	Dizziness	Nausea	Hematuria	Overall incidence
Combination therapy	68	3	8	2	19%
Mono therapy	68	3	2	1	8.8%

## 4. Discussion

### 4.1. The Principle of Phloroglucinol Tamsulosin Combination Therapy in the Treatment of Lower Ureteral Calculi

Lower ureteral calculi is one of the common symptoms of urinary calculi (a common urinary system disease that calculi formed in different parts of the urinary tract [9]). Intracavitary surgery for upper urinary tract stones has been widely applied clinically with the development of intracavitary minimally invasive technology. It has become the first-line surgical procedure for lower urinary tract stones because of its small trauma, safety and effectiveness, replacing most of the open surgery [10]. During minimally invasive intracavitary lithotripsy, it is necessary to continuously infuse fluid into the

renal pelvis. The higher the perfusion pressure and the faster the perfusion speed, the easier it is to maintain a clear vision and remove the crushed stones by accelerated flow through the working sheath, which leads to the increase of the pressure in the renal pelvis. Phloroglucinol is a myotropic, non-atropine and non-papaverine smooth muscle antispasmodic which directly acts on the smooth muscles of the gastrointestinal tract and the urogenital tract with no anticholinergic effect, no symptoms like xerostomia, visual impairment, dysuria, hypotension, increased heart rate, and arrhythmia etc. associated, and no effect on cardiovascular function compared with other smooth muscle antispasmodics [4]. Tamsulosin is usually used for the treatment of BPH to block the  $\alpha_1\text{A}$  adrenergic receptors in the prostate through selective  $\alpha_1$  blockers and relax the smooth muscle of the prostate, thereby relieving related urinary system symptoms, such as dysuria and painful urination etc. [5-8].

#### 4.2. The Effect of Combination Therapy on IL-10 and CRP Levels

IL-10, a recognized inflammatory and immunosuppressive factor, is a multi-cell-derived, multifunctional cytokine that regulates cell growth and differentiation, and participates in inflammatory and immune responses. It plays an important role in tumors, infections, organ transplantation, hematopoietic system and cardiovascular system, and is closely related to blood, digestion, especially cardiovascular diseases [11-12]. C-reactive protein (CRP) test can be used to determine the degree of inflammation in a person's body clinically. The results of this study show that using phloroglucinol combined with tamsulosin to treat patients with lower ureteral calculi can significantly regulate the levels of IL-10 and CRP in them, indicating that it can effectively act on the serum for treatment.

#### 4.3. The Effect of Combination Therapy on Cys-C Level

NGAL is a safety indicator of nephrotoxicity or AKI results after treatment with drug candidates [13]. Cys-C is a cysteine protease inhibitor. It is a low molecular weight and non-glycosylated low protein, expressed in all nucleated cells with a stable growth rate and a constant production rate, and is not affected by age, gender, infection, tumor and diet [14]. Since kidney is the only organ that clears Cys-C from the circulation (metabolized and reabsorbed in the proximal tubule cells and completely degraded in the epithelial cells quickly), it will no longer return to the blood circulation, and it is also not secreted by renal tubules. Therefore, it can be used as an endogenous marker for early response to GFR [15]. The results of this study showed that phloroglucinol tamsulosin combination therapy for lower ureteral calculi patients had significant effect on elevating NGAL and Cys-C levels in patient's body.

#### 4.4. The Effect of Combination Therapy on KIM-1 Level

KIM-1 is a new type I transmembrane glycoprotein which is located in the apical membrane of the renal proximal convoluted tubules and persists in renal tubular epithelial cells. After kidney injury, KIM-1 will highly express in renal proximal convoluted tubule epithelial cells so that can indicate the severity of the injury. It also participates in the early damage and repair of renal tubular epithelial cells, renal interstitial fibrosis, adhesion, apoptotic cell clearance and immune response etc. [16]. In vitro and animal studies have shown that KIM-1 can be a marker for early diagnosis of renal tubular injury with high sensitivity and specificity so it can be used as a simple, sensitive and accurate method to detect early renal injury [17-18]. The results of this study show that combination treatment for patients with lower ureteral calculi can significantly regulate the NGAL, Cys-C and KIM-1 levels in them, indicating that it has positive effect on protease for treatment.

## 5. Conclusion

In conclusion, phloroglucinol tamsulosin combination treatment has significant effect on patients with lower

ureteral calculi. It can effectively regulate the IL-10 and CPR levels, improve the serum and protease levels, increase the expulsion rate and stone diameter and shorten the expulsion time with elevated levels of Cys-C and KIM-1, further improving the protease in the patient's body to achieve optimal effect.

## Acknowledgements

We thank for Zhenshu Wu for assistance Analysis on Efficacy of phloroglucinol tamsulosin combination therapy for medical expulsion of lower ureteral calculi and influence on patients' Cys-C level.

This work was supported by grants from National Natural Science Foundation of China (81802567), Leading Specialist Construction Project- Department of Urology, the First Affiliated Hospital, Jinan University (711006), Medical Scientific Research Foundation of Guangdong Province, China (B2021370).

## References

- [1] Corbo J, Wang J. Kidney et al. *Emerg Med Clin North Am*. 2019 Nov; 37 (4): 637-648.
- [2] Fontenelle LF, Sarti TD. Kidney Stones: Treatment and Prevention. *Am Fam Physician*. 2019 Apr 15; 99 (8): 490-496.
- [3] Yamashita S, Kohjimoto Y, Iguchi T, et al. Ureteral wall volume at ureteral stone site is a critical predictor for shock wavelithotripsy outcomes: comparison with ureteral wall thickness and area. *Urolithiasis*. 2019 Aug 23.
- [4] Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi [J]. *J Urol*, 2005, 174 (1): 167-172.
- [5] Park SC, Jung SW, Lee JW, Rim JS. The effects of tolterodine extended release and alfuzosin for the treatment of double-j stent-related symptoms. *J Endourol* 2009; 23: 1913.
- [6] Yakoubi R, Lemdani M, Monga M, et al. Is there a role for  $\alpha$ -blockers in ureteral stent related symptoms? A systematic review and meta-analysis. *J Urol* 2011; 186: 928.
- [7] Norris RD, Sur RL, Springhart WP, et al. A prospective, randomized, double-blinded placebo-controlled comparison of extended release oxybutynin versus phenazopyridine for the management of postoperative ureteral stent discomfort. *Urology* 2008; 71: 792.
- [8] Beiko DT, Watterson JD, Knudsen BE, et al. Double-blind randomized controlled trial assessing the safety and efficacy of intravesical agents for ureteral stent symptoms after extracorporeal shockwave lithotripsy. *J Endourol* 2004; 18: 723.
- [9] Skolarikos A. Medical treatment of urinary stones. *Curr Opin Urol*. 2018 Sep; 28 (5): 403-407.
- [10] Probst C E, Denstedt J D, Razvi H. Preoperative indications for percutaneous nephrolithotripsy in 2009 [J]. *J Endourol*, 2009, 23 (10): 1557-1561.

- [11] Ouyang W, O'Garra A. IL-10 Family Cytokines IL-10 and IL-22: from BasicScience to Clinical Translation. *Immunity*. 2019 Apr 16; 50 (4): 871-891.
- [12] Xue M, Qiqige C, Zhang Q, et al. Effects of TumorNecrosis Factor  $\alpha$  (TNF- $\alpha$ ) and Interleukina 10 (IL-10) on Intercellular CellAdhesion Molecule-1 (ICAM-1) and Cluster of Differentiation 31 (CD31) in Human Coronary Artery Endothelial Cells. *Med Sci Monit*. 2018 Jun 27; 24: 4433-4439.
- [13] Sun MZ, Chen HM, Zhou ZW, et al. Neutrophil gelatinase-associated apolipoprotein in patients with iodine-contrast nephropathy. *J Biol Regul Homeost Agents*. 2019 Jul-Aug; 33 (4): 1171-1176.
- [14] Otsuka T, Tanaka A, Suemaru K, et al. Evaluation of the clinical application of eystatin C, a new marker of the glomerular filtration rate, for the initial dose-setting of arbekacin [J]. *J Clin PharmThor*, 2008, 33 (3): 227.235.
- [15] Bakoush O, Grubb A, Rippe B, et al. Inaccuracy of GFR predictions by plasma cystatin C in patients without kidney dysfunction and in advanced kidney disease [J]. *Clin Nephrol*, 2008, 69 (5): 331-338.
- [16] Vaidya V S, Ozer J S, Dieterle F, et al. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies [J]. *Nat Biotechnol*, 2010, 28 (5): 478-485.
- [17] Zuo J, Khan A, Glenton P A, et al. Effect of NADPH oxidase inhibition on the expression of kidney injury molecule and calcium oxalate crystal deposition in hydroxyL-proline-induced hyperoxaluria in the male Sprague Dawley rats [J]. *Nephrol Dial Transplant*, 2011, 26 (6): 1785-1796.
- [18] Malyszko J, Koc-Zorawska E, Malyszko J S, et al. Kidney injury molecule-1 correlates with kidney function in renal allograft recipients [J]. *Transplant Proc*, 2010, 42 (10): 3957-3959.