



# The Effect of Terpene Combination on Ureter Calculus Expulsion After Extracorporeal Shock Wave Lithotripsy

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**Purpose:** Terpene combination (Rowatinex) is known to help with the expulsion of urinary stones. The aim of this study was to determine how Rowatinex affects the expulsion of remnant stones after shock wave lithotripsy (SWL).

**Materials and Methods:** Clinical data were collected retrospectively from 499 patients with a diagnosis of ureteral stones who underwent SWL from January 2009 to August 2012. Ureteral stones were diagnosed in all patients by kidney, ureter, and bladder x-ray and abdominal computed tomography (CT). The progress of patients was documented every 2 weeks to confirm remnant stones after SWL. The patients with remnant stones underwent SWL again. Group 1 consisted of patients who were prescribed an analgesic, Tamsulosin 0.2 mg, and Rowatinex. Group 2 consisted of patients who were prescribed only an analgesic and Tamsulosin 0.2 mg. The expulsion rate of urinary stones was compared between groups.

**Results:** The expulsion rate of urinary stones was not significantly different between the two groups after 2 weeks. However, after 4 weeks, group 1 had a significantly higher expulsion rate (72.2% compared with 61.1%,  $p=0.022$ ). Fifteen patients (10.2%) in group 1 and 40 (11.4%) in group 2 had to undergo ureteroscopic removal of the stone ( $p=0.756$ ). Acute pyelonephritis occurred in one patient (0.7%) in group 1 and in one patient (0.3%) in group 2 ( $p=0.503$ ).

**Conclusions:** The long-term administration of Rowatinex for 4 weeks increased the expulsion rate of urinary stones after SWL.

**Keywords:** Lithotripsy; Terpene combination; Urolithiasis

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## INTRODUCTION

Urinary stones are a common illness and account for about 12% of patient visits in urology outpatient departments [1]. The treatment modalities for urinary stones include shock wave lithotripsy (SWL), laparoscopic removal, and percutaneous surgery—all of which are less invasive than open surgery. SWL is noninvasive and does not necessitate general anesthesia or hospital admission. SWL is widely used as a primary treatment of urinary stones because its clinical outcome is good and it can be performed in an outpatient setting [2,3]. Terpene combination (Rowatinex) was developed in the 1950s, and it is known to reduce pain

induced by ureteral stones and to increase the spontaneous passage of urinary stones when used in a supportive role. Bak et al. [4] reported that Rowatinex can reduce the frequency of urinary stone pain and significantly increase early spontaneous expulsion of urinary stones. In this study, we evaluated the effect of Rowatinex on the expulsion rate of ureteral stones after SWL.

## MATERIALS AND METHODS

### 1. Patients

Clinical data were collected retrospectively from 499 patients with a diagnosis of ureteral stones who underwent

**TABLE 1.** Characteristics of the patients in the two groups

Characteristic	Group 1 <sup>a</sup> (n=147)	Group 2 <sup>b</sup> (n=352)	p-value
Age (y)	48.32±14.14	48.20±14.46	0.933
Sex (male:female)	106:41	234:118	0.247
Stone size (mm)	7.49±3.11	7.25±2.80	0.317
No. of stone location (%)			0.425
Upper ureter	104 (70.7)	230 (65.3)	
Mid ureter	6 (4.1)	22 (6.3)	
Lower ureter	37 (25.2)	100 (28.4)	

<sup>a</sup>:Taken nonsteroidal anti-inflammatory drugs (NSAIDs), Tamsulosin 0.2 mg and Rowatinex. <sup>b</sup>:Taken NSAIDs and Tamsulosin 0.2 mg.

SWL at a single center between January 2009 and August 2012. All patients had urinary stones larger than 4 mm in size. Patients with a nonfunctioning kidney, severe retractable pain, multiple urinary stones, severe hydronephrosis, a serum creatinine level greater than 2.5 mg/dL, a history of urinary tract surgery, ureteral stricture, or a ureteral stent or who were pregnant were excluded [5]. We also excluded patients who had remnant stones, but had not undergone a second SWL. All patients were instructed to consume plenty of water and to exercise. Patients with severe consistent pain and those who showed no change in stone size underwent ureteroscopic removal of stone (URS).

## 2. Methods

### 1) Protocol

The magnetic-type ASADAL-M1 (COMED, Seongnam, Korea) shock wave lithotripter was used. SWL was performed at a rate of 3,000 to 4,000 times per session. The power of the SWL was increased gradually from AC120V to AC170V and was controlled on the basis of the patient's status. All patients underwent SWL at their initial visit. The progress of the patients was documented 2 weeks after the initial SWL to confirm any remnant stones. Patients with remnant stones underwent SWL again. The patients were re-evaluated 4 weeks after the initial SWL. Tramadol 50 mg was administered intramuscularly to all patients for pain control. We subdivided the patients into two groups according to their prescription. Group 1 included patients who were prescribed an analgesic, Tamsulosin 0.2 mg, and Rowatinex; group 2 included patients who were prescribed an analgesic and Tamsulosin 0.2 mg but not Rowatinex. The patients were instructed to take one Rowatinex capsule three times a day.

### 2) Data collection

Ureteral stones were diagnosed by kidney, ureter, and bladder x-ray (KUB) and abdominal computed tomography (CT). The size of ureteral stones was calculated based on the major axis length on the abdominal CT image. All patients were instructed to look closely for expelled ureteral stones during urination. The patients were asked to

document the date of expulsion of any stones and any adverse effects of the prescribed medications. Successful expulsion of ureteral stones was defined as the absence of ureteral stones on KUB or abdominal CT images.

We compared the age, sex, size and location of ureteral stones, number of SWL sessions, and treatment duration between the two groups. We re-evaluated the expulsion rate of ureteral stones every 2 weeks after the initial SWL.

### 3. Statistical analysis

PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A chi-square test and Student t-test were performed, and a p value of <0.05 was deemed significant.

## RESULTS

Group 1 included 147 patients (106 men and 41 women). The mean age of group 1 was 48.32±14.14 years (18–80 years). A total of 352 patients (234 men and 118 women) were not prescribed Rowatinex (group 2). The mean age of group 2 was 48.20±14.46 years (19–84 years). The mean size of ureteral stones was 7.49±3.11 mm in group 1 and 7.25±2.80 mm in group 2 (p=0.317) (Table 1). In group 1, 104 patients (70.7%) had upper ureteral stones, 6 patients (4.1%) had mid ureteral stones, and 37 patients (25.2%) had lower ureteral stones. In group 2, 230 patients (65.3%) had upper ureteral stones, 22 patients (6.3%) had mid ureteral stones, and 100 patients (28.4%) had lower ureteral stones (p=0.425) (Table 1).

Two weeks after the initial SWL, expulsion of ureteral stones was observed in 55 patients (37.4%) in group 1 and in 125 patients (35.5%) in group 2 (p=0.684) (Fig. 1). A total of 319 patients without stone passage were re-evaluated at their third visit 4 weeks after the initial SWL. The age, sex, stone size, and stone location were not significantly different between the two groups (Table 2). The cumulative expulsion rate of ureteral stones in group 1 was higher than that in group 2 (72.2% compared with 61.1%, p=0.022) (Fig. 1). The mean number of SWL sessions was 1.63±0.49 in group 1 and 1.64±0.48 in group 2 (p=0.645). The treatment duration, complications, and number of patients who underwent URS were not significantly different between the

two groups (Table 3). Adverse effects occurred after SWL in a total of 74 patients (14.8%): 23 patients (15.6%) in group 1 and 51 patients (14.5%) in group 2 ( $p=0.783$ ). Five patients in group 1 and nine patients in group 2 experienced hematuria ( $p=0.422$ ). Acute pyelonephritis occurred in one patient (0.7%) in group 1 and in one patient (0.3%) in group

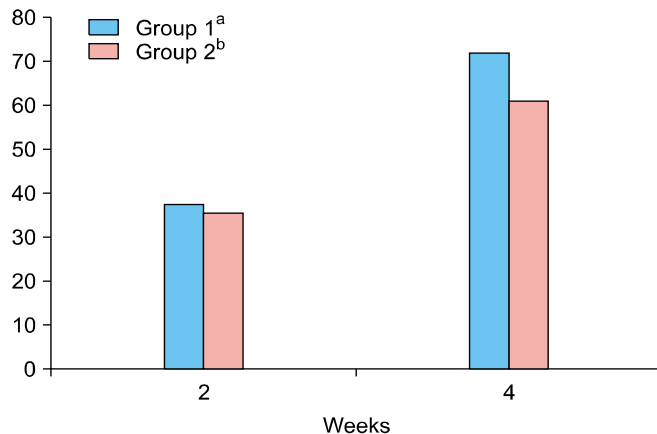
2 ( $p=0.503$ ). Fifteen patients (10.2%) in group 1 and 40 patients (11.4%) in group 2 had to undergo URS ( $p=0.756$ ).

## DISCUSSION

The treatment modalities for ureteral stones are determined based on the size, number, and location of the urinary stones in the urinary tract. Because of recent technological advances in surgical instruments, the treatment of ureteral stones has become more diversified. SWL, open surgery, and URS are widely being performed. Medical expulsive therapy can be applied when the size of the stones is small [6].

After Chaussy et al. [3] introduced SWL for the treatment of urinary stones in 1980, SWL has become the primary treatment modality for urinary stones. SWL is a non-invasive treatment of urinary stones. However, stone expulsion does not occur immediately after SWL; rather, the debris is released slowly for about 1 month. The remnant stones may cause obstruction, recurrent infection, or calculus regrowth [7].

Medical treatment has been proven to be effective at inhibiting stone growth and recurrence of urinary stones [8,9]. Previous studies have reported that Rowatinex can help with the removal of remnant stone after SWL [10]. Rowatinex is an essential oil of terpenic type that consists of pinene (3%), camphene (15%), borneol (10%), anethol (4%), and cineol (3%). Rowatinex is used for the treatment



**FIG. 1.** Comparison of expulsion rate (%). 2 weeks: Cumulative expulsion rate 2 weeks after first SWL, 4 weeks: Cumulative expulsion rate 4 weeks after first SWL. <sup>a</sup>:Taken NSAIDs, Tamsulosin 0.2 mg and Rowatinex. <sup>b</sup>:Taken NSAIDs and Tamsulosin 0.2 mg. NSAID, nonsteroidal anti-inflammatory drug; SWL, shock wave lithotripsy.

**TABLE 2.** Characteristics of patients in the two groups at the second shock wave lithotripsy

Characteristic	Group 1 <sup>a</sup> (n=92)	Group 2 <sup>b</sup> (n=227)	p-value
Age (y)	49.16±13.98	48.73±14.50	0.805
Sex (male:female)	65:27	153:74	0.598
Stone size (mm)	6.15±3.02	5.68±2.56	0.195
No. of stone location (%)			0.232
Upper ureter	71 (77.1)	167 (73.6)	
Mid ureter	2 (2.2)	16 (7.0)	
Lower ureter	19 (20.7)	44 (19.4)	

<sup>a</sup>:Taken nonsteroidal anti-inflammatory drugs (NSAIDs), Tamsulosin 0.2 mg and Rowatinex. <sup>b</sup>:Taken NSAIDs and Tamsulosin 0.2 mg.

**TABLE 3.** Comparison of therapeutic outcomes between the two groups

Variable	Group 1 <sup>a</sup> (n=147)	Group 2 <sup>b</sup> (n=352)	p-value
Cumulative expulsion rate 2 wk after first SWL	55 (37.4)	125 (35.5)	0.684
Cumulative expulsion rate 4 wk after first SWL	104 (72.2)	206 (61.1)	0.022
Sessions	1.63±0.49	1.64±0.48	0.645
Treatment duration (d)	52.03±113.18	43.67±104.77	0.443
Complications	23 (15.6)	51 (14.5)	0.783
Conversion to URS <sup>c</sup>	15 (10.2)	40 (11.4)	0.756

Values are presented as number (%) or mean±standard deviation.

SWL, shock wave lithotripsy.

<sup>a</sup>:Taken nonsteroidal anti-inflammatory drugs (NSAIDs), Tamsulosin 0.2 mg and Rowatinex. <sup>b</sup>:Taken NSAIDs and Tamsulosin 0.2 mg. <sup>c</sup>:The number of patients who were performed ureteroscopic removal of stone (URS).

of ureteral stones, kidney stones, renal colic, and other urologic conditions [11-13].

The exact mechanism of action of Rowatinex is not yet fully known. In preclinical experiments, it was confirmed that Rowatinex has antilithogenic, antibacterial, anti-inflammatory, spasmolytic, and analgesic properties [14, 15]. The antilithogenic property, which influences renal oxalate lithogenesis, is important because most urinary stones are composed of calcium oxalate aggregates. Inhibition of remnant stone formation originating after SWL might increase the long-term success rate of SWL [16]. In addition, Rowatinex has shown antibacterial effects against a variety of pathogens [10]. Rowatinex has anti-inflammatory and analgesic properties derived from cineole and anethole, which are important to patients who have urolithiasis with spasm, inflammation, pain, and infection [17,18]. According to Horvath [19], Rowatinex and its single terpenes—such as camphene, cineole, and borneol—have antispasmodic effects on smooth muscle preparations in animal models. Djaladat et al. [7] reported that Rowatinex increases urine excretion by increasing renal blood flow and has antispasmodic effects that may help with the expulsion of renal stone. Engelstein et al. [11], in their prospective, randomized, and double-blind study, showed that the expulsion rate of ureteral stones in the Rowatinex group was greater than that in the placebo group in 87 patients in the emergency room (81% compared with 59%). However, the number of subjects in that study was small, and the authors did not consider stone size and treatment duration. In a randomized trial conducted by Romics et al. [10], the expulsion rate of urinary stones was greater and the treatment duration was shorter in the Rowatiex group than in the placebo group; no significant differences in age, sex, or stone size were found between the two groups. The expulsion rate of urinary stones 2 weeks after the initial SWL was not significantly different between the two groups (37.4% compared with 35.5%,  $p=0.684$ ). However, 4 weeks after the initial SWL, the cumulative expulsion rate of ureteral stones in group 1 was greater than that in group 2 (72.2% compared with 61.1%,  $p=0.022$ ). This result indicates that Rowatiex was not effective at stone expulsion in the short term, but was effective over a treatment period of 4 weeks.

This finding may be explained by the properties of Rowatinex, which increases urine excretion and has an antispasmodic effect. The number of SWL sessions and the treatment duration were not significantly different between groups. The occurrence rate of complications after SWL was not significantly different between the two groups (Table 3).

Fifteen patients (10.2%) in group 1 and 40 patients (11.4%) in group 2 underwent URS because of consistent colicky pain or little effect of SWL ( $p=0.756$ ) (Table 3). Acute pyelonephritis, which may have been induced by SWL, occurred in one patient (0.7%) from group 1 and in one patient (0.3%) from group 2 ( $p=0.503$ ). Other adverse effects, such as diarrhea, nausea, and vomiting, were not observed.

This study is meaningful because it was a pilot study of the effects of Rowatinex on the expulsion of remnant urinary stone after SWL in Korea. This study had several limitations. First, SWL was not performed by a single operator and the observation period was only 4 weeks. Second, we were unable to routinely analyze the stone components expelled by patients with ureteral stones because it was difficult to retrieve them from the patients. Therefore, we could not determine the relationship between the stone component and the effect of Rowatinex. Third, we did not assess pain; therefore, we could not determine whether Rowatinex reduced colicky pain. Fourth, the analgesic and Tamsulosin prescribed with Rowatinex may have influenced the effects of Rowatinex. Last, the results of this study are based on a retrospective review. Thus, confounding factors and measurement bias were not able to be reduced as much as they could have been in a prospective or randomized study. Additional studies from multiple centers are thus warranted.

## CONCLUSIONS

Rowatinex was effective at increasing the expulsion rate of ureteral stones 4 weeks after the initial SWL. Rowatinex may increase the long-term success rate of SWL, especially when used for more than 4 weeks without significant adverse effects.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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