

# Efficacy of Naftopidil as a Medical Expulsive Therapy in Japanese Men With Ureteral Stones: A Prospective Randomized Controlled Study

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## Abstract

**Background:** Naftopidil combined with an antispasmodic agent and a supplement that facilitates stone expulsion has reportedly produced an increased rate of ureteral stone expulsion. A randomized controlled study was conducted to determine the efficacy of naftopidil as a medical expulsive therapy for male patients with ureteral stones.

**Methods:** Male patients (n = 500) with stones from the upper to the lower ureter were randomized to one of four groups and followed for 1 month to assess spontaneous passage of stones. The control group received only analgesics. The other three groups received daily doses of 240 mg flopropione, an antispasmodic agent and 1,350 mg extract of *Quercus salicina* Blume/*Quercus stenophylla* Makino (QS), a supplement that facilitates stone expulsion; 50 mg naftopidil; or 50 mg naftopidil in combination with 240 mg flopropione and 1,350 mg QS. Stone expulsion and characteristics were evaluated by urinalysis; kidney, ureter and bladder X-ray; ultrasound; and computed tomography.

**Results:** The probability of expulsion of ureteral stones < 6 mm increased 1.570-fold (95% confidence interval (CI): 1.039 - 2.374, P < 0.05) with naftopidil compared to control; the probability of expulsion of a lower ureteral stone < 6 mm increased 1.778-fold (95% CI: 1.066 - 2.965, P < 0.05) with naftopidil compared to control. None of the stones > 6 mm spontaneously passed.

**Conclusions:** For relatively small ureteral stones < 6 mm, analgesic treatment combined with naftopidil would be the first choice. However, for relatively large ureteral stones > 6 mm, it appears that analgesia is sufficient for initial treatment of ureteral stone.

**Keywords:** Naftopidil; Ureteral stone; Medical expulsive therapy

## Introduction

Ureteral stones are common. The annual disease rate of upper urinary tract stones was 137.9 per 100,000 population according to an epidemiological investigation of urinary calculus conducted in Japan in 2015, which is an approximately three-fold increase over that reported in an investigation in 1965 [1]. Most patients with ureteral stones visit hospitals due to renal colic. Non-steroidal anti-inflammatory drugs (NSAIDs) and non-narcotic pain-relievers are administered. The pain is often controlled within several hours, but placement of indwelling ureteral stents may be urgently indicated when severe pain continues. When the spontaneous passage of ureteral stones is expected, patients are advised to maintain a high water intake, and spasmolytic drugs and drugs facilitating stone expulsion are often prescribed.

It has been recently reported that  $\alpha$ 1-blockers facilitate ureteral stone expulsion [2]. The stimulation of  $\alpha$ 1-adrenergic receptors increases ureteral peristaltic frequency, smooth muscle tonus and contractile force, resulting in ureteral spasm and decreased ureteral flow [3]. The  $\alpha$ 1-adrenergic receptor consists of three subtypes:  $\alpha$ 1A-,  $\alpha$ 1B- and  $\alpha$ 1D-adrenergic receptors. It is thought that  $\alpha$ 1A-adrenergic receptors are widespread in the proximal urethra, prostate and bladder outflow. The  $\alpha$ 1B-adrenergic receptors are found more often in the vascular smooth muscles, and  $\alpha$ 1D-adrenergic receptors are predominantly found in the detrusor. Therefore,  $\alpha$ 1A- and  $\alpha$ 1D-blockers were originally used for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia and neurogenic bladder. Further, the existence of  $\alpha$ 1-receptors has been demonstrated in the human ureter. While  $\alpha$ 1A-,  $\alpha$ 1B- and  $\alpha$ 1D-receptors exist in the ureter, the  $\alpha$ 1D-receptor is widely distributed from the proximal to distal ends. Higher expression of  $\alpha$ 1A-,  $\alpha$ 1B- and  $\alpha$ 1D-receptors has been demonstrated in the distal ureter than the proximal ureter [4, 5].

Some reports have described the effectiveness of naftopidil for ureteral stone expulsion [6-11]. When various  $\alpha$ 1-blockers, such as urapidil, tamsulosin and naftopidil, were administered to patients with ureteral stones to determine their efficacy for stone expulsion, naftopidil in combination with an antispasmodic agent and a supplement that facilitates stone expulsion produced a significantly increased rate of ureteral stone expulsion [12]. However, one study reported that naftopidil did not

Manuscript submitted April 27, 2019, accepted May 13, 2019

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doi: <https://doi.org/10.14740/jocmr3843>

increase spontaneous stone passage rates or reduce analgesic use [13]. This prospective, multicenter, randomized controlled study was therefore designed to clarify the effect of naftopidil for medical expulsive therapy (MET), including the factors of stone size and position.

## Materials and Methods

Patient databases from Nippon Medical School Musashi Kosugi Hospital, Ookurayama Memorial Hospital, Minami Machida Hospital, Kitamurayama Hospital and Asao General Hospital were analyzed. From July 2007 to December 2017, 500 patients with a unilateral ureteral stone < 10 mm in size were enrolled; 335 patients completed the study. All patients were diagnosed as having ureteral stones by urinalysis; ultrasonography; and kidney, ureter and bladder X-ray (KUB). Non-contrast computed tomography (CT) or drip infusion pyelography (DIP) was performed when necessary. The ureteral stones were classified as upper ureteral (U1), medial ureteral (U2) and lower ureteral (U3). U1 was defined as a stone located below the ureteropelvic junction to the upper border of the iliac crest. U2 was defined as a stone overlapping the ilium. U3 was defined as a stone located below the lower border of the sacroiliac joint to the ureterovesical junction. The exclusion criteria included multiple stones, severe hydronephrosis, urinary tract infection, a history of ureteral surgery, renal colic more than 24 h in duration, diabetes mellitus, hypotension, previous spontaneous stone expulsion and a history of intake of an  $\alpha$ -adrenergic blocker or calcium antagonist. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee.

The 500 patients were placed randomly into one of four groups of 125 patients each. Patients in group A were given analgesics as required. Patients in group B were given 240 mg flopropione and 1,350 mg extract of *Quercus salicina* Blume/*Quercus stenophylla* Makino (QS) once daily. Patients in group C were given 50 mg naftopidil once daily. Patients in group D were given 240 mg flopropione, 1,350 mg QS extract and 50 mg naftopidil once daily. A total of 335 patients completed this study. All patients were told to drink at least 2 L of water daily. The four groups were followed for 30 days. Urinalysis, KUB and ultrasonography were performed on days 1, 14, and 28. NSAIDs were administered to control the onset of acute renal colic. Medication side effects were carefully documented during the treatment period.

Discrete variables are presented as counts or frequencies and were evaluated by the Chi-square or Fisher's exact test. Skewed data are summarized as the median and interquartile range (IQR), and were analyzed with the Mann-Whitney U test. The Cox proportional hazards regression model was applied to estimate the effects of different variables on stone expulsion. The statistical software "EZR" (Easy R) was used for all analyses [14]. All statistical tests were based on two-tailed probability with  $P < 0.05$  considered statistically significant. The sample size was sufficient to achieve a statistical power of 95% at 5% type I error.

## Results

Table 1 shows the patient characteristics. A total of 335 patients completed the study; 38 patients in group A, 39 patients in group B, 44 patients in group C and 44 patients in group D were lost to follow-up or arbitrarily withdrew. Medication side effects appeared in five patients. Extracorporeal shock-wave lithotripsy was performed in 54 patients, and 24 patients received indwelling ureteral stents due to pyelonephritis and pain. Transfer to the hospital occurred in four patients and four patients withdrew due to treatment of other diseases. The average patient ages in the control; flopropione and QS extract; naftopidil, flopropione and QS extract; and naftopidil groups were 48.3, 45.7, 48.8 and 45.9 years old, respectively, and the average stone sizes were 5.1, 5.1, 5.1 and 4.9 mm, respectively. There were no significant differences in age, stone size, or stone position among the groups (Table 1). In all cases, the mean expulsion times for each group were 20.0, 22.6, 16.8 and 17.8 days, respectively. In all U1 cases, the mean expulsion times for each group were 23.5, 25.2, 20.1 and 19.5 days, respectively. In all U2 cases, the mean expulsion times for each group were 27.3, 24.0, 24.2 and 23.3 days, respectively. In all U3 cases, the mean expulsion times for each group were 17.4, 19.5, 13.4 and 16.0 days, respectively. There were no significant differences between U1 and U2 cases. There were significant differences between groups A and C in all cases and in all U3 cases ( $P < 0.05$ ).

In all cases, multivariate analysis with a Cox proportional hazards model indicated that the probability of expulsion was 0.638 times higher (95% confidence interval (CI): 0.429 - 0.948) in group B than in group A ( $P < 0.05$ ), and 1.426 times higher (95% CI: 1.000 - 2.033) in group C than in group A ( $P < 0.05$ ), while group D compared with group A did not demonstrate an increased probability of expulsion. In U3 cases, the probability of expulsion was 1.555 times higher (95% CI: 1.013 - 2.388) in group C than in group A ( $P < 0.05$ ), while the other groups compared with group A did not demonstrate an increased probability of expulsion. Naftopidil in combination with an antispasmodic agent and the QS supplement (as administered to treatment group D) previously has produced a significantly increased rate of ureteral stone expulsion. In all cases, U1 and U3, multivariate analysis with a Cox proportional hazards model indicated that the probability of expulsion was 2.183 times higher (95% CI: 1.475 - 3.229), 2.403 times higher (95% CI: 1.220 - 4.733) and 2.064 times higher (95% CI: 1.249 - 3.409) in group C than in group B, respectively. In all cases and U1 cases, the probability of expulsion was 1.962 times higher (95% CI: 1.323 - 2.910) and 2.542 times higher (95% CI: 1.298 - 4.979) in group D than in group B (Table 2).

Multivariate analysis with a Cox proportional hazards model indicated an increased probability of expulsion of stones measuring less than 6 mm (Table 3). In all cases, the probability of expulsion was 1.570 times higher (95% CI: 1.039 - 2.374) in group C than in group A ( $P < 0.05$ ). In U3 cases, the probability of expulsion was 1.778 times higher (95% CI: 1.066 - 2.965) in group C than in group A ( $P < 0.05$ ), while group C compared with group B demonstrated the probability of expulsion in all ureteral stone and U3 stone cases.

Multivariate analysis with a Cox proportional hazards

**Table 1.** Patient Characteristics and Clinical Outcomes in the Four Treatment Groups

	Group				P value
	A	B	C	D	
	Analgesics only	<i>Quercus salicina</i> + flopropione	Naftopidil	<i>Quercus salicina</i> + flopropione + naftopidil	
Randomized patients (n)	125	125	125	125	
Withdrawal patients (n)	38	39	44	44	
Self-withdrawal	18	18	18	20	
Side effect	1	1	2	1	
Extracorporeal shock-wave lithotripsy	12	13	15	14	
Ureteral stent	5	6	7	6	
Hospital change	1	0	1	2	
Treatment of other diseases	1	1	1	1	
Analyzed patients (n)	87	86	81	81	NS
Age, years, mean (SD)	48.3 (12.5)	45.7 (13.6)	48.8 (10.9)	45.9 (10.8)	NS
Stone size, mm, mean (SD)	5.1 (1.6)	5.1 (1.9)	5.1 (1.8)	4.9 (1.9)	NS
Stone location (n)					
Right/left	40/47	33/53	42/39	33/48	NS
Proximal	27	42	33	33	NS
Middle	6	6	5	4	NS
Distal	54	38	43	44	NS
Duration of passage, days, mean (SD)	20.0 (9.8)	22.6 (9.3)	16.8 (9.9)*	17.8 (10.3)	NS *0.040
Proximal	23.5 (8.7)	25.2 (8.1)	20.1 (10.4)	19.5 (10.5)	NS
Middle	27.3 (6.5)	24.0 (9.4)	24.2 (7.3)	23.3 (7.3)	NS
Distal	17.4 (9.7)	19.5 (9.9)	13.4 (8.6)*	16.0 (10.2)	NS *0.041

The difference of each group compared with analgesic only group was shown in analyzed patients, patient age, stone size, stone location and duration of passage. \*Analgesics only versus naftopidil group. NS: not significant; SD: standard deviation.

model indicated the probability of expulsion of stones measuring 6 mm or more (Table 4). None of the ureteral stones measuring 6 mm or more had facilitated spontaneous passage, while groups C and D compared with group B demonstrated the probability of expulsion in all ureteral stone cases.

## Discussion

Spontaneous passage of ureteral stones less than 10 mm in longer diameter can be expected. Murakami et al reported that stones in the lower ureter more easily expel spontaneously; approximately 50% of lower ureteral stones are expelled spontaneously within 1 month after diagnosis and about 90% are expelled within 4 months [15]. Pain control and diuresis by drinking water are important for facilitating spontaneous passage of ureteral stones. Conservative therapy in Japan has commonly involved QS extract and flopropione with NSAIDs to reduce the ureteral spasms that induce stone stagnation, promote stone expulsion and alleviate renal colic.

QS extract has been clinically used in Japan since 1969 in the treatment of urolithiasis as an alternative medicine that facilitates the spontaneous expulsion of ureteral stones [16]. QS

extract promotes stone discharge in a rat ureteral stone model [17], has a diuretic effect in urolithiasis patients [15], dissolves calcium phosphate crystals and prevents crystal growth at a silk thread nucleus in the rat bladder [18], and has an effect in preventing stone formation and recurrence in urolithiasis patients [19]. The stone composition in the four groups was mainly calcium oxalate or a mixture of calcium oxalate and calcium phosphate. Therefore, it is likely that there was little effect of the QS extract except on the stones containing calcium phosphate. The effect of flopropione as an antispasmodic agent on the rate of passing a calculus from the urinary tract has been compared retrospectively with patients in whom passage was spontaneous. Flopropione was shown to be superior to the control in cumulative passage rate after initiation of treatment [20]. Flopropione has been shown to exert a spasmolytic effect not only on smooth muscle of the gastrointestinal tract but also on smooth muscle of the pancreaticobiliary and urinary systems [21].

It has been reported that  $\alpha 1$ -receptors exist not only at the edge of the ureter but also in the upper and medial ureter. Itoh et al evaluated the  $\alpha 1A$ -,  $\alpha 1B$ - and  $\alpha 1D$ - subtype mRNA with real-time reverse transcription polymerase chain reaction and immunohistochemical staining using ureteral specimens of 20

**Table 2.** Cox Proportional Hazards Model: Multivariate Analysis for the Probability of Overall Stone Expulsion in Each Ureteral Position

	Hazard ratio	95% CI	P value
Whole ureter			
A vs. B	0.638	0.429 - 0.948	0.0262
A vs. C	1.426	1.000 - 2.033	0.0497
B vs. C	2.183	1.475 - 3.229	< 0.0001
A vs. D	1.267	0.886 - 1.814	NS
B vs. D	1.962	1.323 - 2.910	0.0008
Proximal			
A vs. B	0.766	0.348 - 1.687	NS
A vs. C	1.805	0.870 - 3.746	NS
B vs. C	2.403	1.220 - 4.733	0.0113
A vs. D	1.915	0.928 - 3.953	NS
B vs. D	2.542	1.298 - 4.979	0.0065
Middle			
A vs. B	1.158	0.163 - 8.238	NS
A vs. C	2.259	0.371 - 13.76	NS
B vs. C	1.650	0.275 - 9.906	NS
A vs. D	3.283	0.523 - 20.60	NS
B vs. D	2.170	0.360 - 13.08	NS
Distal			
A vs. B	0.708	0.437 - 1.146	NS
A vs. C	1.555	1.013 - 2.388	0.0440
B vs. C	2.064	1.249 - 3.409	0.0047
A vs. D	1.082	0.699 - 1.675	NS
B vs. D	1.494	0.901 - 2.478	NS

A: analgesics only. B: daily doses of 240 mg flopropione and 1,350 mg QS. C: daily dose of 50 mg naftopidil. D: daily dose of 240 mg flopropione, 1,350 mg QS and 50 mg naftopidil. CI: confidence interval; NS: not significant.

patients that underwent nephroureterectomy [5]. In the proximal and medial ureter, the distribution of  $\alpha 1$ -adrenoreceptors was  $\alpha 1D \geq \alpha 1A > \alpha 1B$ . In the distal ureter, the distribution of  $\alpha 1$ -adrenoreceptors was  $\alpha 1D > \alpha 1A > \alpha 1B$ . Sun et al reported that daily administration of 50 mg naftopidil, a selective  $\alpha 1D$ -blocker, increased the distal ureteral stone expulsion rate 5.263-fold compared to the control [6]. Ohgaki et al showed that 50 mg naftopidil in combination with 240 mg flopropione and 1,350 mg QS extract once daily compared with 0.2 mg tamsulosin or 30 mg urapidil with these drugs significantly increased the ureteral stone expulsion rate 2.38-fold compared to 240 mg flopropione and 1,350 mg QS extract once daily [12]. Kohjimoto et al showed that 75 mg naftopidil once daily significantly increased distal ureteral stone expulsion rate to 1.78 times that of 240 mg flopropione once daily [10]. The rationale for the administration of naftopidil in this study is that the  $\alpha 1D$  receptor is widely distributed from the proximal to distal ureter [5].

**Table 3.** Cox Proportional Hazards Model: Multivariate Analysis for the Probability of Expulsion of Stones < 6 mm in Each Ureteral Position

	Hazard ratio	95% CI	P value
Whole ureter			
A vs. B	0.751	0.477 - 1.183	NS
A vs. C	1.570	1.039 - 2.374	0.0329
B vs. C	2.000	1.270 - 3.150	0.0028
A vs. D	1.145	0.759 - 1.727	NS
B vs. D	1.513	0.963 - 2.377	NS
Proximal			
A vs. B	0.704	0.271 - 1.825	NS
A vs. C	1.617	0.707 - 3.698	NS
B vs. C	2.363	0.999 - 5.586	NS
A vs. D	1.385	0.622 - 3.085	NS
B vs. D	2.028	0.881 - 4.670	NS
Distal			
A vs. B	0.775	0.453 - 1.328	NS
A vs. C	1.778	1.066 - 2.965	0.0275
B vs. C	2.105	1.190 - 3.724	0.0105
A vs. D	1.115	0.672 - 1.849	NS
B vs. D	1.396	0.793 - 2.456	NS

A: analgesics only. B: daily doses of 240 mg flopropione and 1,350 mg QS. C: daily dose of 50 mg naftopidil. D: daily dose of 240 mg flopropione, 1,350 mg QS and 50 mg naftopidil. CI: confidence interval; NS: not significant.

Anticholinergic (antimuscarinic) drugs are used in clinical urology to treat bladder motor hyperreflexia and renal or ureteral colic, based on the hypothesis that an antimuscarinic drug would decrease hypercontractility and spasms of the bladder and ureter. However, there is no preclinical evidence that the continuous use of anticholinergic medication for an extended period for bladder hyperreflexia results in upper urinary tract dilation, as shown in an animal model [22].

It has been reported that scopolamine treatment does not affect renal colic or spontaneous passage of stones; ureteral peristalsis did not increase even after scopolamine was injected intravenously [23].

For the whole range of ureteral stone types, the addition of naftopidil to flopropione and QS extract therapy was predicted to facilitate stone expulsion, as in the previous study. This study additionally includes a control (follow-up) group and naftopidil-alone group. The addition of naftopidil to flopropione and QS extract therapy significantly facilitated stone expulsion regardless of stone size. Flopropione and QS extract therapy compared with the control did not appear to facilitate stone expulsion. Naftopidil alone slightly facilitated stone expulsion compared to controls through the overall range of ureteral stones, U3 stones and overall ureteral stones less than 6 mm. From these results, it appears that flopropione and QS extract therapy has a negligible effect on the overall probabil-

**Table 4.** Cox Proportional Hazards Model: Multivariate Analysis for the Probability of Expulsion of Stones > 6 mm in Each Ureteral Position

	Hazard ratio	95% CI	p value
Whole ureter			
A vs. B	0.514	0.228 - 1.159	NS
A vs. C	1.345	0.662 - 2.732	NS
B vs. C	2.621	1.197 - 5.735	0.0159
A vs. D	1.518	0.732 - 3.148	NS
B vs. D	2.961	1.325 - 6.617	0.0081
Proximal			
A vs. B	1.465	0.296 - 7.261	NS
A vs. C	2.683	0.541 - 13.30	NS
B vs. C	1.894	0.610 - 5.881	NS
A vs. D	2.855	0.521 - 15.64	NS
B vs. D	2.007	0.565 - 7.133	NS
Distal			
A vs. B	0.486	0.157 - 1.511	NS
A vs. C	1.316	0.564 - 3.073	NS
B vs. C	2.641	0.822 - 8.493	NS
A vs. D	1.009	0.425 - 2.400	NS
B vs. D	2.107	0.648 - 6.857	NS

A: analgesics only. B: daily doses of 240 mg flopropione and 1,350 mg QS. C: daily dose of 50 mg naftopidil. D: daily dose of 240 mg flopropione, 1,350 mg QS and 50 mg naftopidil. CI: confidence interval; NS: not significant.

ity of stone expulsion.

Evaluation according to location of the ureteral stones showed no effect of any treatment compared to controls for the middle and upper ureteral stones, and that naftopidil alone slightly promoted ureteral stone expulsion compared with controls for the lower ureteral stones. Naftopidil alone was effective in promoting smaller, lower ureteral stone expulsion, but all therapies were ineffective in overall upper ureteral stone or larger stone expulsion. The investigation of stone expulsion effect by ureteral stone size showed that naftopidil alone compared with the addition of naftopidil to flopropione and QS extract therapy significantly facilitated stone expulsion through the whole range of overall ureteral stones less than 6 mm (Table 3). There was no effect of any treatment compared to the control group through the whole range of overall ureteral stones of 6 mm and larger (Table 4). From these results, it appears that conventional treatment with anticholinergic agents may possibly retard stone expulsion.

Considering that no group was involved in promoting expulsion of larger stones, the involvement of  $\alpha 1$  receptors may be limited in stone expulsion in the cases of ureteral stones 6 mm in size or larger. Neither  $\alpha 1$  blockers nor other expulsive promoter drugs promote ureteral peristalsis; therefore, even though the  $\alpha 1$  blocker is known to have a ureteral dilation effect, this may be the reason these therapies failed to promote

stone expulsion.

For the whole range of ureteral stones, naftopidil alone, the addition of naftopidil to flopropione and QS extract therapy, and follow-up only facilitated stone expulsion compared with flopropione and QS extract therapy; ineffectiveness of stone expulsion by flopropione and QS extract was apparent. Further, compared to the control treatment with only NSAIDs and analgesics, the stone expulsion effect of naftopidil was not as high as expected. The role of flopropione and QS extract, which have been prescribed in Japan for many years, may need to be reconsidered for promoting stone expulsion. For relatively small lower ureteral stones, administration of naftopidil in addition to administration of NSAIDs for pain relief might be necessary. However, naftopidil might not be necessary for relatively large stones.

### Limitations

A limitation of the present study was the unexpectedly high drop-out rate. However, I was still able to observe some effect of naftopidil as an MET. Also, the study included only male patients because of restrictions regarding the use of naftopidil in the Japanese insurance system. Although the number of patients enrolled was small, the results will be helpful to medical doctors considering naftopidil as an MET for patients with a ureter stone.

### Conclusions

In MET, the need for antispasmodic agents is limited, as they appear to delay the excretion of ureteral stones. For relatively small ureteral stones, analgesic treatment combined with naftopidil would be the first choice. However, for relatively large ureteral stones, additional interventions for symptomatic patients would be necessary.

### Acknowledgments

None to declare.

### Financial Disclosure

No funding was received for the publication of this study.

### Conflict of Interest

The author declares that there is no conflict of interest associated with the work described in the manuscript.

### Informed Consent

All patients provided valid informed consent.

## Author Contributions

The author was involved in patient care and wrote or edited the manuscript.

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