The evaluation of the effectiveness of Gilaburu (*Viburnum opulus* L.) extract in the medical expulsive treatment of distal ureteral stones

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ABSTRACT

Objective: Medical expulsive therapy is an important non-invasive treatment modality that facilitates the passage of ureteral stones. The aim of the present study was to evaluate the efficacy of Gilaburu (*Viburnum opulus*) extract in the treatment of distal ureteral stones <10 mm.

Material and methods: Data of 103 patients were retrospectively analyzed. Patients were divided into two groups: those given *V. opulus* 1000 mg peroral 3×2 and diclofenac 50 mg peroral on-demand (n=53) and those given only diclofenac sodium 50 mg peroral on-demand (n=50). Comparisons of stone expulsion rates and the elapsed time until the expulsion between the groups were determined as primary outcome measures. The comparison of the need for additional treatment [ureteroscopy (URS) or extracorporeal shock wave lithotripsy (ESWL)], the need for emergency admission, analgesic requirement, and the complication rates in additional treatment were determined as secondary outcome measures.

Results: The mean age of the patients was 45.8±14.5 years. The rate of stone expulsion was significantly higher (82% vs. 66%, p=0.026), and elapsed time to stone expulsion was significantly shorter (9±1.8 vs. 14±2.3 day, p=0.018) in the *V. opulus* group. The need for additional treatment (URS and ESWL) and analgesic requirement was less in the *V. opulus* group (9.4% vs. 20%, p=0.038 and 24.5% vs. 44%, p=0.042, respectively).

Conclusion: *V. opulus* is an herbal treatment alternative that facilitates the passage of ureteral stones <10 mm. Prospective, randomized studies are needed to support these results.

Keywords: Medical expulsive treatment; ureteral stone; *Viburnum opulus*.

Introduction

Urolithiasis is one of the most common urological diseases affecting 5%–10% of the people worldwide.[1] Of all urinary tract stones, 20% are located in the ureter, and 70% are located in the lower third of the ureter.[2]

A stone entering the ureter and causing a sudden increase in the pelvicalyceal system pressure is responsible for colic pain.[3] While some patients with ureteral stones are asymptomatic, some may have serious pain and seek treatment. A spontaneous passage is expected in the majority of ureteral stones. The size and location of the stone are the two most important factors predicting the stone passage.[4] Passage rates for stones <5 mm were reported at 68%, whereas rates for stones >5–10 mm were reported at ≤47%.[5]

It has been shown that medical expulsive therapy (MET), in particular, using alpha-blockers can facilitate stone passage.[6] MET has many benefits; it can reduce the severity and duration of symptoms caused by ureteral stones and can prevent complications, such as urinary tract infection, hydronephrosis, and loss of renal function. It may also reduce the need for more invasive procedures, such as surgical treatment and extracorporeal shock wave lithotripsy (ESWL), and may reduce complications arising from these procedures. It can also provide more efficient and economical use of restricted health system resources, such as clinician time and hospital beds.[7]

Both European and American guidelines recommend MET for stones <10 mm.[8,9] MET can be applied for patients who do not have abso-

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lute indications (infection, refractory pain, and deterioration of renal function) for active stone removal. Alpha-blockers, such as tamsulosin and silodosin and phosphodiesterase-5 inhibitors (PDE5Is), are the primary agents used for MET.[2,10] Among the calcium channel blockers, nifedipine is one of the agents used for MET purposes. These agents are used in different urological diseases, and they are also used for ureteral dilation and passage of stones due to the physiological characteristics of the ureter muscle.[11] These treatments can be applied alone or in combination. However, a study comparing monotherapy with combination therapy has not yet been conducted. Their efficacy was comparable in the majority of studies comparing these agents, and their superiority to each other was assessed according to their side effect profile.[12,13] Significant side effects, such as hypotension and retrograde ejaculation with alpha-blockers, and visual and cardiac disorders with the use of PDE5Is may occur.[14,15]

Viburnum opulus L. is a plant extract promising to protect patients from these side effects and to provide an alternative effective treatment method for distal ureteral stones <10 mm.[16] It has been shown in preclinical studies that this plant, which grows widely in Central Anatolia, has antioxidant, antiurolithiatic, antispasmodic, anti-inflammatory, and antinociceptive effects.[17,18] The aim of the present study was to analyze the efficacy of *V. opulus*, an alternative herbal treatment method, in distal ureteral stones <10 mm. To the best of our knowledge, this is the first clinical trial evaluating the efficacy of *V. opulus* in the treatment of ureteral stones.

Material and methods

Patient selection

Data of 103 patients who were referred to two different urology clinics due to distal ureteral stones <10 mm between January 2017 and June 2018 were retrospectively analyzed. All these patients were consecutive. The study was conducted in accordance with the principles of the Declaration of Helsinki. Consent was obtained from all patients to use their data for scientific studies, provided that their identities are kept confidential.

Patients >18 years, with distal ureteral stones 5–10 mm in diameter, and with radiopaque stones were included in the study. The stones under the iliac vessels in the imaging methods were regarded as distal. Patients who had ureteral stone in solitary kidney, bilateral ureteral stones, concomitant kidney stones, urinary tract anomalies, previous ureteral surgery, peptic ulcer history, anuria, hydronephrosis accompanied by high fever, chills, shivering symptoms in the kidney where the ureteral stone is located, radiolucent stones, nausea, and/or vomiting that would prevent oral treatment, high creatinine values, severe pain unresponsive to medical treatment, known allergy to the planned treatment, liver and/or renal failure; who used other drugs, such as diuretics and calcium channel blockers; with previous spontaneous stone passage; with diabetes; and who were lactating mothers and pregnant women were excluded from the study. Five patients who developed dyspeptic complaints due to *V. opulus* and eight patients who were lost to follow-up were also excluded from the study. All patients included in the study had sterile urine culture at the beginning of treatment.

Patient groups and study protocol

Patients were divided into two groups as those given *V. opulus* 1000 mg peroral 3×2 and diclofenac sodium 50 mg peroral *on-demand* (n=53) and those given only diclofenac sodium 50 mg peroral *on-demand* (n=50). Data of the patients within 4 weeks from the treatment initiation were analyzed. Patients were initially diagnosed with non-contrast computerized tomography (NCCT). The kidney, ureter, and bladder X-ray (KUB) was initially applied to confirm that the stones were radiopaque. Patients were checked weekly by KUB after diagnosis. Confirmation with NCCT was performed in patients whose KUB was suspicious. If the stone passed within the study period, the day the stone passed was accepted as the endpoint of the study for that patient, and the passage was confirmed with a KUB. Since only patients with opaque stones were included in the study, KUB was used as the imaging method for control purposes. Patients whose stone did not pass within 30 days were considered as unresponsive to medical treatment, and alternative therapies [ureteroscopy (URS) or ESWL] were planned for these patients. Patients were recommended to increase hydration. Informed consent was obtained from the patients. The study flowchart is shown in Figure 1.

Data collection and outcome measures

Patient's demographic data, stone, and treatment data were collected from patient files. Comparisons of stone expulsion rates and the elapsed time until the expulsion between the groups were determined as primary outcome measures. The comparison of the need for additional treatment (URS or ESWL), the need for emergency admission, analgesic use, and the complication rates that were seen in additional treatment were determined as secondary outcome measures.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences 23.0 package program (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics are expressed as mean, standard deviation, median, lowest, highest, frequency, and ratio values. Kolmogorov–Smirnov test was used to measure the distribution of variables. Independent samples t-test and Mann–Whitney U test were used for analysis of quantitative independent data. Chi-square test was used for analysis of qualitative independent data. A p-value <0.05 was considered statistically significant.

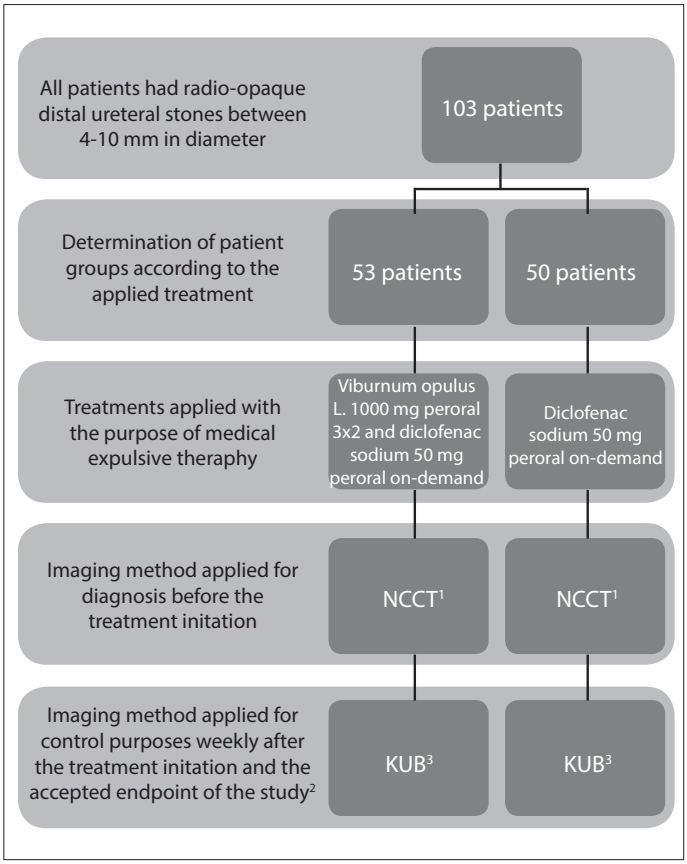

Figure 1. Study flowchart
[1]Non-contrast computerized tomography
[2]If the patient passed his/her stone before the planned control time, the end point of the study was considered as the day when the patient passed the stone
[3]Kidney, ureter, bladder X-ray

Table 1. Patients' demographic and treatment data

Variables	Min–max	Median	Mean±SD/n (%)
Patient age (year)	21–75	44	45.8±14.5
Gender			
Female			42 (40.8%)
Male			61 (59.2%)
Stone size (mm)	4–10	7.1	7.4±1.8
Overall expulsion rate			78 (75.7%)
Elapsed time until expulsion (day)	5–20	12	13±3.8
Need for additional treatment			15 (14.6%)
Need for emergency admission			77 (75%)
Need for analgesic use			35 (34%)
Complication rate			15 (14.2%)

min: minimum; max: maximum; SD: standard deviation

Results

Of the 103 patients, 61 were male. The mean body mass index of the patients was 23.7±4.4 kg/m^2. In both groups, the mean stone size was 7.4±1.8 mm. The overall expulsion rate was 75.7% (n=78), and the elapsed time to expulsion was 13±3.8 days. Additional treatments were needed in 14.6% (n=15) of the patients, and 75% of the patients required emergency admissions. Overall, demographic data and MET outcomes are summarized in Table 1.

Demographic data were similar in the combination treatment group (*V. opulus*+diclofenac *on-demand*) and diclofenac *on-demand* group. Stone size was also similar in both groups (7.4±1.4 vs. 7.5±1.8, p=0.628). The rate of stone expulsion was significantly higher in the combination group (82% vs. 66%, p=0.026). The elapsed time to stone expulsion was significantly shorter in the combination group (9±1.8 days vs. 14±2.3 days, p=0.018). The need for additional treatment (URS and ESWL) was less in the combination group (9.4% vs. 20%, p=0.038). There was no significant difference between the two groups with regard to emergency service admission and complication rates in additional treatment (p=0.545 and p=0.488, respectively). The analgesic requirement rate was significantly lower in the *V. opulus* group (24.5% vs. 44%, p=0.042). The comparison of demographic data and treatment outcomes of the combination and diclofenac groups is given in Table 2.

The most frequent reason for emergency admission was renal colic, which was refractory to medical treatment in 62 (80.5%) patients. The findings of pyelonephritis in 12 (15.6%) patients and urosepsis in 3 (3.9%) patients with hypotension and high fever were other reasons for emergency admission. The most common complication after additional treatments was colic pain in 11 (73.4%) of 15 patients. Two (13.3%) patients had minor ureteral perforation during URS, and 2 (13.3%) patients developed urinary tract infection requiring hospitalization. Minor gastric complaints were seen in 12 patients treated with *V. opulus*. Eight patients had tolerated, but the treatment had to be terminated in five patients in consequence of those gastric complaints, and these patients were excluded from the study.

Discussion

Observation with periodic evaluation of patients with ureteral stones <10 mm and whose symptoms are under control is an appropriate approach for initial treatment. Interest in conservative treatment has increased in recent years considering the cost and complication rates of minimally invasive treatments used in the treatment of ureteral stones. The location, size, number, structure of the stone, and symptoms of the patient adjust the treatment of ureteral stones. Since ureteral spasm, anatomy, and

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Table 2. Comparison of two groups with regard to demographic data, stone characteristics, and treatment data

Variables	*V. opulus*+diclofenac on-demand group (n=53)		Diclofenac on-demand group (n=50)		p
	Mean±SD/n (%)	Median	Mean±SD/n (%)	Median	
Patient age (year)	43.8±13.6	44	42.4±14.2	42	0.508[a]
Gender					
Female	22 (40.7%)		20 (40.8%)		0.725[b]
Male	31 (59.3%)		30 (59.2%)		
Stone size (mm)	7.4±1.4	7.1	7.5±1.8	7.1	0.628[c]
Overall expulsion rate	44 (82%)		34 (66%)		***0.026***[b]
Elapsed time until expulsion (day)	9±1.8	10.8	14±2.3	12.6	***0.018***[c]
Need for additional treatment	5 (9.4%)		10 (20%)		***0.038***[b]
Ureteroscopy	4 (80.0%)		7 (70.0%)		
Extracorporeal shock wave lithotripsy	1 (20.0%)		3 (30.0%)		
Need for emergency admission	37 (69.8%)		40 (80%)		0.545[b]
Need for analgesic use	13 (24.5%)		22 (44%)		***0.042***[b]
Complication rate	7 (13.2%)		8 (16%)		0.488[b]

[a]Independent samples t-test. [b]Chi-square test. [c]Mann–Whitney U test. Significant p values are given in bold and italics.

mucosal edema due to inflammation predict the rate of expulsion, the goal of conservative treatment is to cope with these factors. The aim of the MET is to relax the ureteral smooth muscle without inhibiting the ureteral peristalsis, to increase the rate of stone passage, and to shorten the stone passage duration by eliminating the patient's symptoms.

Following the identification of alpha 1 receptors in the human ureter in 1970 by Malin et al.[11], the idea that blockade of these receptors can reduce the basal tone, reduce the intraluminal pressure, and increase the chance of stone expulsion has gained importance.[19] Tamsulosin, which is widely used in the treatment of benign prostatic hyperplasia, is the first alpha-blocker used for this purpose. Tamsulosin, a combined alpha 1d and alpha 1a androgen receptor blocker, has been shown to increase stone expulsion rates, to reduce pain, and to shorten the time to stone expulsion compared with placebo.[2,19] In a recent multicenter, randomized, double-blind, placebo-controlled study involving 3450 patients, tamsulosin was found to facilitate the passage of distal ureteral stones significantly and to relieve renal colic.[20] Then, silodosin, a more selective alpha-blocker, has begun to be used for this purpose. Silodosin provided better stone expulsion rates and stone expulsion time than tamsulosin.[12] In many meta-analyses published between 2013 and 2015, it was reported that the rate of stone clearance increased with different alpha-blockers (tamsulosin, silodosin, and alfuzosin), and the expulsion time accelerated.[21,22] However, alpha-blockers have also been shown to increase the risk of major side effects according to the subgroup analysis of placebo-controlled trials and main analysis.[6] On the other hand, a randomized clinical trial suggesting that tamsulosin did not increase passage for ureteral located stones <9 mm was recently published. In this study, 512 patients were randomized to tamsulosin and placebo arms, and no significant difference was observed between the two groups with regard to stone passage rates.[23]

PDE5Is sildenafil and tadalafil cause cyclic guanosine monophosphate (cGMP) increase and ureteric muscle relaxation by the nitric oxide/cGMP signaling pathway. Thus, it facilitates the passage of stones with a similar effect to alpha-blockers.[13] These drugs may also have side effects, such as flushing, headache, dyspepsia, and nasal congestion due to vasodilator effects.[24] In addition, PDE5Is are contraindicated with nitrate therapy and may lead to severe hypotension.[25] Owing to the undesirable side effects of these agents, "off-label" use for stone expulsion, and because they cannot be prescribed in women, clinicians are directed to alternative treatments for conservative treatment of ureteral stones.[8]

Viburnum is a plant species that grows in an endemic region from South America to Southeast Asia with 230 different species.[26] Gilaburu is a traditional drink prepared from *V. opulus*, which is one of the four species of *Viburnum* that grows in Turkey. Owing to the antioxidant and antimicrobial properties possessed by the components of the *V. opulus* plant, beneficial effects in different organ systems have been demonstrated.[27-29] Beneficial effects on the gastrointestinal mucosa due to antioxidant properties have been suggested.[30] Altun et al.[31] showed the hepatopro-

tective and hypoglycemic activities of *V. opulus* plant in rats in their experimental study. They suggested that this effect is due to the contents, such as glycosides, terpenes, and polyphenols, that the extract contains. Antioxidative and free radical-scavenging properties of chlorogenic acid in *Viburnum* species have been demonstrated in vitro. Chlorogenic acid may protect against cardiovascular diseases. Similar effects have been shown in *Viburnum* species. In addition, *Viburnum* strains have antitumor and antibacterial effects due to their polyphenolic content.

Owing to the beneficial effects of *V. opulus*, it was thought that it could have a place in the treatment of urolithiasis, and many preclinical and experimental studies have been conducted on this subject.[17] These studies have revealed positive results and promised that the plant can be used in the conservative treatment of ureteral stones.[32] The World Health Organization recommends that herbal medicines could be used, as well as traditional medicines, because of their low cost and low side effect profiles. *V. opulus* is expected to facilitate the passage of the stone because of the relaxant, spasmolytic, and anticholinesterase properties of chlorogenic acid.[33] In Turkish folk medicine, the juice is obtained by squeezing the *V. opulus* fruit, and it is used to pass kidney stones.[34]

Ilhan et al.[17] have found that the lyophilized juice of *V. opulus* has diuretic and antiurolithiatic features that are caused by the inhibitor effects on oxalate levels and free radical production in their experimental studies in which they constituted artificial urolithiasis in rats. This plant contains triterpenoids, iridoids, diterpenoids, sesquiterpenes, coumarins, anthocyanins, phenolic acids, and organic acids, and they suggested that the biological activity of the plant can be related to these substances.[18] They concluded that the results they obtained with this study can constitute scientific evidence for the traditional use of *V. opulus* for the passage of ureteral stones.

It has been shown that *V. opulus* can be used in the medical treatment of patients with hypocitraturic stone with contained electrolyte concentrations. *V. opulus* juice and lemon juice, a natural source of citrate, were compared. Potassium was found to be higher, and sodium and calcium were found to be lower in *V. opulus*. No significant difference was found with regard to magnesium and citrate levels. *V. opulus* appears to be an alternative pharmaceutical treatment method in patients with stone with mild-to-moderate hypocitraturia due to the presence of citrate as much as lemon juice.[35] These results indicate that *V. opulus* may help to prevent stone formation due to antioxidant effects and citrate and potassium contents, as well as to facilitate stone passage through antispasmodic and relaxant effects. *V. opulus* can have smooth muscle antispasmodic effect via scopoletin. The chemical structure of scopoletin is shown in Figure 2. Animal studies have shown that *V. opulus* has an antispasmodic effect on the uterus and has a relaxing effect on the human uterine tissue in clinical trials.[36] It has been suggested that these plant extracts may be used in the treatment of premenstrual syndrome. In our study, the effect of facilitating the passage of ureteral stones could possibly be due to scopoletin.

In the literature, stone expulsion rates between 70.2% and 88% have been reported for distal ureteral stones <10 mm using different alpha-blockers.[37,38] In our study, it was possible to achieve a similar rate (82%) with *V. opulus*, a purely herbal agent. Periods about the duration of stone expulsion ranging from 8 to 21 days were reported in different studies.[38,39] In our study, the mean expulsion duration with *V. opulus* was similarly 9±1.8 days. In addition, we found that the need for analgesic was significantly less in the group using *V. opulus*. We think that this is due to the antinociceptive and anti-inflammatory effects of the plant, which was emphasized by Altun et al.[18] earlier. In the present study, the mean age of the patients was 45 years, and the mean age was similar between the two groups. Dellabella et al.[40] found that age is not a predictive factor in the study comparing three different agents for MET purposes. The mean stone size between the two groups was also comparable. We consider that this similarity between the groups prevented a selection bias because the ureteral stone dimension is an important factor for spontaneous passage.[4] All of the stones in our study were located in the distal ureter. Since the majority of the MET studies performed to date are directed to distal ureteral stones, we have included only distal-located stones.

The retrospective nature and relatively few patient numbers are the main limitations of our study. Another drawback is that the citrate level in the 24-hour urine was not measured, as one of the effects of *V. opulus* was to increase the urine citrate level. We also did not evaluate all patients with NCCT for control purposes. We did not perform NCCT in asymptomatic patients with normal KUB. Finally, the lack of a placebo group for control is also a limitation. To our knowledge, this is the first clinical study evaluating the effect of *V. opulus* on the passage of distal ureteral stones <10 mm. Prospective, randomized, placebo-controlled trials are required to confirm the results of our study.

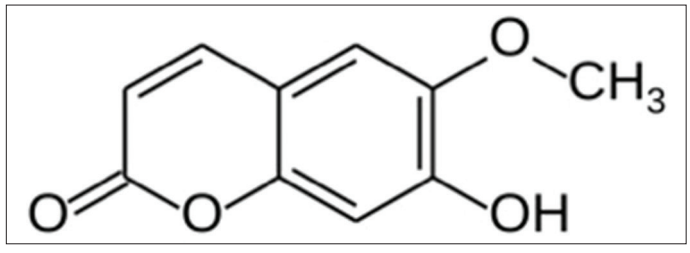

Figure 2. Scopoletin phytochemical that is responsible for the antispasmodic effect of *Viburnum opulus*

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In our study, we found that distal ureteral stones <10 mm had higher expulsion rates and had shorter passage duration in the group treated with *V. opulus* and diclofenac than in the group treated with only diclofenac. In addition, the need for additional treatment was less in the first group. We concluded that *V. opulus* is an important herbal treatment option in the MET of ureteral stones.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.K., V.Ü., O.Ç.; Design – F.K., V.Ü., O.Ç.; Supervision – V.Ü., O.N.; Resources – F.K., V.Ü., O.Ç., T.Ö., Ö.Ç., E.C., O.N.; Materials – F.K., V.Ü., O.Ç., T.Ö., Ö.Ç., E.C., O.N.; Data Collection and/or Processing – F.K., V.Ü., O.Ç., T.Ö., Ö.Ç.; Analysis and/or Interpretation – F.K., V.Ü., O.Ç., T.Ö., Ö.Ç., E.C., O.N.; Literature Search – F.K., V.Ü.; Writing Manuscript – F.K., V.Ü.; Critical Review – V.Ü., O.N.

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