The effect of an herbal agent "Tutukon®" on the spontaneous passage rates of ureteric stones

Bitkisel bir ajan "Tutukon®"un üreter taşlarının spontan pasaj oranlarına etkisi

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Özet

Amaç: Bu çalışmanın amacı, bir bitkisel ajan olan Tutukon®' un 5-10 mm üreter taşlarının spontan geçiş oranları üzerindeki etkinliğini değerlendirmektir.

Gereç ve Yöntemler: 5-10 mm çapında, tek radyoopak üreter taşı olan 96 hasta randomize olarak iki gruba ayrıldı. Grup 1'e (n=51) konservatif yaklaşıma ek olarak 45 mg/gün (üç kez) Tutukon®, Grup 2' deki hastalar (n=45) ise 4 haftalık takip süresince klasik konservatif yaklaşımla takip edildi. Taş geçiş oranları, taş çıkarma süreleri, haftalık kolik ataklarındaki değişim ve kolik ağrısı nedeniyle hastaneye yeniden başvuru oranları karşılaştırıldı.

Bulgular: Taş çıkarma oranları iki grup arasında istatistiksel olarak anlamlı farklılık gösterdi (%66.7'ye karşı %46.7, p = 0.048). Ek olarak, Tutukon® alan vakalarda, sadece konservatif önlemler alan Grup 2 hastaları ile karşılaştırıldığında, taşların spontan geçişi için gereken ortalama süre anlamlı olarak kısaydı (sırasıyla 5,79 ± 2,39 ve 8,82 ± 3,48 gün) (p = 0,001). Benzer şekilde, takip süresi boyunca ortalama renal kolik atakları Grup 1 hastalarında önemli ölçüde azaldı (sırasıyla %66,6'ya karşı %36, p = 0,001). Son olarak Grup 1'de kolik ağrı ataklarının daha az olduğu görüldü ve "Tutukon®"un bir diğer avantajı da taşların üreterin daha distal kısmına yer değiştirmesiydi (%35.2'ye karşı %4).

Sonuç: Üreter taşlarının medikal tedavisinde Tutukon® kullanımı, taşların spontan düşüş oranlarını hızlandırabilir ve aynı zamanda üreterin daha alt seviyelerine geçişini hızlandırabilir.

Anahtar Kelimeler: bitkisel ajanlar; medikal terapi; spontan pasaj; üreter taşları

Abstract

Objective: The objective of this study is to assess the efficacy of an herbal agent (Tutukon®) on the spontaneous passage rates of ureteral calculi 5-10 mm.

Material and Methods: 96 patients having a single radio-opaque ureteral stone 5-10 mm were randomized into two groups. Group 1 (n = 51) received Tutukon®, 45 mg/day (three times) in addition to the conservative approach and Group 2 patients (n = 45) were followed with the classical conservative approach during 4 weeks of follow-up. The stone passage rates, stone expulsion time, change in weekly colic episodes and hospital readmission rates for colicky pain were compared.

Results: Stone expulsion rates showed a statistically significant difference between the two groups (66.7 % vs 46.7 %, p = 0.048). Additionally mean time period required for the spontaneous passage of the calculi was meaningfully short in those cases receiving Tutukon® when compared with Group 2 patients undergoing conservative measures only (5.79 ± 2.39 vs 8.82 ± 3.48 days, respectively) (p = 0.001). Similarly, the mean renal colic episodes during the follow-up period were significantly diminished in Group 1 patients (66.6 vs 36%, p = 0.001, respectively). Lastly, colic pain attacks were noted to be less in Group 1, and another advantage of "Tutukon®" was the relocation of the stones to a more distal part of the ureter (35.2 vs 4 %).

Conclusion: Use of Tutukon® in the medical management of ureteral calculi can accelerate the spontaneous passage rates and also relocate them into the lower portion of the ureter.

Keywords: Herbal agents; medical therapy; spontaneous passage; ureteral stones

The study was approved by Ethics Committee of Clinica Endourologica Timisoara (Approval number: 02.05.2018/137). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

7 - 10 % of the population suffers from urolithiasis and related problems[1,2]. Ureteric stones should be detected and removed as quickly as possible to prevent obstruction and the associated discomfort of colic. This is the case regardless of where the calculus is located in the urinary system (3,4).

Although the likelihood of spontaneous passage of larger ureteral stones (> 10 mm) is decreased, in asymptomatic cases without obstruction, a conservative approach with pain management and medical expulsive therapy (MET) are reasonable options. Also, compared to minimally invasive surgical procedures, these approaches are safer and less expensive (2). Conservative management, including the use of MET when there is adequate evidence (5,6) is recommended by both the EAU and the AUA guidelines.

As a herbal agent, Tutukon® (Laboratorio Miguel&Garriga, S.A. Barcelona, Spain) is composed of eight different plants. Components of the medication individually show anti-apoptotic, nephroprotective, antioxidant, anti-apoptotic, and spasmolytic effects(7,8). The diuretic, spasmolytic, and anti-inflammatory actions of plant extracts from Opuntia ficus indica (9), Rosmarinus officinales (10), and Cynodon dactylon[11] have all been studied for their potential effects on stone formation.

The present study aimed to investigate the possible effects of an herbal agent, "Tutukon®" on the spontaneous passage rates of ureteral stones and related factors.

MATERIAL AND METHODS

From December 2017 to December 2018, 96 patients were enrolled (58 men, 38 females, M/F: 1.52) with a single radio-opaque ureteral stone (5-10 mm). Patients with multiple ureteral stones, bilateral stones, renal stones, severe hydronephrosis, a solitary kidney, a surgical history, diabetes, hypertension, pregnancy, or renal failure were excluded from this study. The protocol for the study was approved by the institution's Ethical Committee, and all participants supplied written informed consent after being given thorough information regarding the herbal substance.

X-ray, abdominal sonography, and plain X-ray (KUB) are all examples of imaging modalities that can be used to examine the urinary system (NCCT).

As a result of these assessments, the 96 patients were split into two groups: Group 2 (n = 45) received the standard conservative treatment (adequate hydration, increased physical activity, and routine pain management with nonsteroidal anti-inflammatory drugs), while Group 1 (n = 51) received a herbal agent (Tutukon®, 45 ml/day) for the same 4-week follow-up period.

If a patient's radiographic evidence of kidney stone passage occurred during this time period, treatment was stopped. In case there was any doubt about the stone's purported spontaneous transit, an NCCT was carried out in addition to the standard video evidence (KUB). Shock wave lithotripsy (SWL) and ureteroscopy will be used to remove a stone if the patient is unable to pass it on their own or if removal of the stone is deemed required due to severe colic pain, the development of hydronephrosis, infection, or hematuria.

Success rates in passing stones, the average time to expel stones, number of weekly colic episodes, and adverse effects were measured in both patient groups.

Herbal Agent

Tutukon® Neo, a herbal supplement produced by the Spanish company Laboratorio Miquel Y Garriga, SA in Barcelona, is always made using the same exact ingredients. Essential fatty acids, flavonoids, polysaccharides, the flavonoid quercetin, and boldin are all present. The components have been studied extensively and found to provide a wide variety of health benefits, including nephroprotective, diuretic, anti-inflammatory, antioxidant, antibacterial, and spasmolytic actions. The drug is available in a hidrolate form and comes in bottles of 250 milliliters. Ideally, adults should take three 7-ml doses daily. Components include 1.413 milligrams of flowers from Sideritis angustifolia, 1.413 milligrams of Melissa officinalis, 1.413 milligrams of flowers from Opuntia ficus-indica, 2.327 milligrams of flowers from Rosmarinus officinalis, and 4.738 milligrams of the aqueous distillate of the dried parts of an Enguisetum arvensis

stem.

Statistical evaluation: SPSS version 22.0 was used for the statistical evaluation (SPSS Inc., Chicago, IL, USA). The presentation of continuous variables was as mean and standard deviation. When a normal distribution was not seen in these variables, the median and IQR were used to present the data. These variables were compared using either a Mann-Whitney U-test or an independent T-test. Categorical variables were expressed using numbers and percentages (%). The Fisher's exact or Chi-square test was used to compare these variables. For all statistical studies, a p-value of <0.05 was used.

RESULTS

A total of 96 people took part in the study (Group 1: 51; Group 2: 45). There were 58 men and 38 women in Group 1 (M/F = 1.52), with a mean age of 36.9±11.3 and 33.2±7.2 in Group 2. Table 1 displays that there was no significant difference between the two groups with regard to the patient (age, gender), stone (size, position), and data. Although few patients experienced mild side effects during the follow-up period, no one stopped taking the medication due to these problems.

The following are the findings from our examination of data collected from both sets of participants: Patients who were given "Tutukon®" (66.7% expulsion rate) had a significantly better outcome than those who were given conservative therapy without medication (46.7% expulsion rate; p = 0.048) in the analysis of the most relevant parameter. Furthermore, it indicated that those in Group 2 who did not get "Tutukon®" passed their ureteric stones more quickly than those in Group 1. Tutukon® significantly accelerated the average time needed for spontaneous transit of calculi compared to Group 2 patients who were treated with just conservative measures (p=0.001). As a result, "Tutukon®" medication facilitated the transit of ureteric stones at a higher rate than conservative treatment alone, resulting in the cases becoming stone-free in a short period (Figure 1).

No statistically significant difference in the mean number of colic attacks was found between the two groups after diligent follow-up for four weeks using only conservative strategies for treating the discomfort (Table 1).

However, when comparing patients in Group 2 who received no specific medication other than conservative management measures with those in Group 1, those who received "Tutukon®" had a significantly higher rate of improvement in the degree of hydronephrosis (delta grade changes), indicating that the dilatation of the upper tract resolved more quickly and effectively in the former group. This finding once again revealed the patent spasmolytic advantages of "Tutukon®" which, throughout the 4-week follow-up period, normalized the urine flow in most cases [1.47 (0.82-2.74) vs. 1.31 (0.73-1.94), p: 0.210].

Stones migrated and relocated from the proximal ureter to the lower ureter in 6 of 17 cases (35.2%), compared to the extremely limited cases in Group two (1 of 24 cases, 4%), suggesting that "Tutukon® application" has additional benefits beyond simply increasing the rate of spontaneous stone passage. The use of "Tutukon®" appears to aid in the migration of stones from the upper to the lower ureter, offering urologists a major advantage in the event of no spontaneous passage and making stone removal more feasible.

When medication and conservative care failed to get the stone to pass on its own, doctors in both groups turned to SWL (in 5 cases) and URS (in 28 cases) to break up the obstruction (3 SWL in Group 1 and 2 in Group 2, 17 URS procedure applied in Group 1 and 11 in Group 2 cases). The classification of Spontaneous Passage rates according to stone localization is given in Table 2.

Modest and transient side effects were reported by patients taking "Tutukon®" including nausea in 9 patients, vomiting in 1 patient, an inability to taste in 3 patients, dysuria in 5 patients, and headache in 5 patients, according to follow-up evaluations of adverse effects. At the end of the follow-up period, seven patients in Group 2 reported only dysuria. These modest and transient side effects did not cause any patients to withdraw from the research and stop treatment.

Table 1. Evaluation of patient and stone related parameters along with the treatment outcomes in both groups

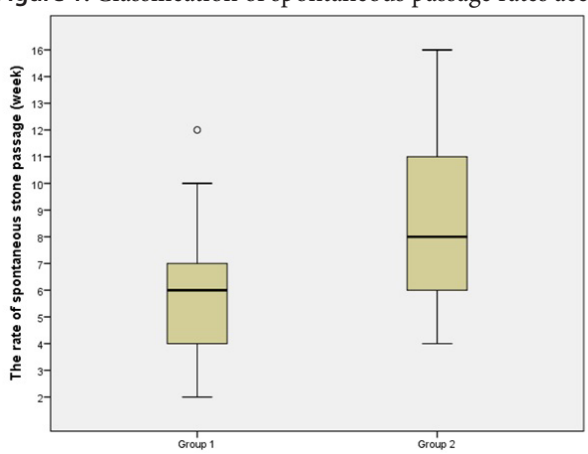
		Group 1 (n: 51)	Group 2 (n:45)	P Value
Gender (Male/ Female)		32(62%)/19(38%)	26(57%)/19(43%)	0.619
Age (mean; year ± SD)		36.9 ± 11.3	33.2 ±7.2	0.067
Stone size (mm± SD)		0.73±0.15	0.70 ± 0.14	0.423
Stone localization	Proximal ureter	21 (41.2 %)	20(44.4 %)	0.945
	Distal ureter	16 (31.4 %)	13 (28.9 %)	
	Vesicoureteral junction	14 (27.5 %)	12 (26.7 %)	
The rate of spontaneous stone passage n (%)		34 (66.7 %)	21 (46.7 %)	**0.048**
Mean number of colic pain/weeks during follow-up period	1. Week	1.69 ± 0.78	1.36 ±0.57	0.220
	2. Weeks (median-IQR)	0.52 (0.31-0.83)	0.39 (0.261.08)	0.756
	3. Weeks	1.49 ± 0.61	1.69 ± 0.46	0.802
	4. Weeks	1.45 ±0.67	1.56 ± 0.54	0.490
	Total	5.24 ± 0.95	5.15 ±1.24	0.710
Improvement of the degree of hydronephrosis (Delta grade) (median-IQR)		1.47 (0.82-2.74)	1.31 (0.73-1.94)	0.210
Need for JJ insertion or ureteroscopy		8 (15.7 %)	8(17.8 %)	0.784
Mean time to spontaneous stone passage(week ± SD)		5.79 ± 2.39	8.82 ± 3.48	**0.001**

Abbreviations: *SD, Standart Deviation*

Table 2. Classification of spontaneous passage rates according to stone localization

	Group 1	Group 2
Proximal Ureter	47.6 % (10/21)	25.0 % (5/20)
Distal Ureter	75.0 % (13/16)	53.8 % (7/13)
Vesicoureteral	85,7% (11/14)	75.0 % (9/12)

Figure 1. Classification of spontaneous passage rates according to stone localization



Group 1: Patient receiving "Tutukon" medication addition to conservative measures

Group 2: Patients receiving only conservative measures

DISCUSSION

Ureteral stone disease, or urolithiasis, affects 2-3% of the population and has a high recurrence rate of around 50%[1]. In order to prevent functional and morphological problems in the kidney, prompt decompression is required in patients with ureteric stones referring to emergency rooms with varying degrees of obstruction in the renal collecting system. Patients for whom conservative treatment does not provide adequate symptom relief or fail to result in the spontaneous passage of the stone(s) may also require stone removal (12). With respect to the likelihood of spontaneous passage in patients treated with conservative treatment, a meta-analysis found that stones 5 mm and 5-10 mm had spontaneous passage rates of 68 and 47%, respectively, with a 95% confidence interval of 46-85% (13). Available data show that the size and location of the ureteral stone have a significant impact on both the success rate of expulsion and the length of time for spontaneous passage. It was shown that the size of the stone is a strong indicator of spontaneous passage rates. Although spontaneous passage is documented in 71%-98% of distal ureteral stones 5 mm, only 25%-51% of stones 5 mm pass without intervention (14).

When considering the risks of traditional treatment methods (such as open surgery, extracorporeal shock wave lithotripsy, and ureteroscopy), physicians looked for less invasive options like "medical expulsive therapy" (MET) to increase the proportion of patients with asymptomatic ureteral calculi who pass the stone on their own during a monitored observation period[15]. Numerous medications have been used, but only alpha-1 blockers were the most commonly used ones for this purpose (15,16). These medications include calcium channel blockers, prostaglandins production inhibitors, glyceryl trinitrate, and steroids. These medications were shown to inhibit ureteral spasms by decreasing the peristaltic frequency and blocking ureteral wall basal tone (7). Alpha-1 blockers have been shown in multiple studies (9,10,17) to be an effective and safe treatment for ureteral stones. While the European Association of Urology (EAU) guidelines advocate MET for all ureteral stones, the current AUA guidelines announced in May 2016 only prescribe treatment for patients with distal ureteral stones 10 mm (6,18).

Other benefits of MET described by the number of well-conducted studies include increased rates of spontaneous passage; a shorter stone passage duration was observed (9,19,20) a considerable reduction in the need for minimally invasive procedures, less unpleasant pain episodes with lower VAS scores, and reduced demand for analgesics (2,21,22).

Reviewing the relevant literature, we find that herbal medicine has been increasingly important in treating and preventing urinary stones during the past few decades in relation to the medical management of stones with an emphasis on medical expulsive therapy. Phytotherapy has been shown in multiple studies to significantly enhance the effects of lithotripsy, increase spontaneous passage rates, and improve the efficacy of urinary tract stone prevention in the conservative treatment of urolithiasis (17). Several of these herbal components show therapeutic potential for the facilitation of spontaneous passage and the treatment of colic discomfort (23), in addition to avoiding crystallization and the formation of new stones. Because of the beneficial effects observed when using these medicines, they are widely employed for the treatment, prevention, and prophylaxis of urolithiasis. These agents were deemed beneficial due to the fact that their active components allowed them to perform multiple functions while posing a minimal danger of unwanted side effects. Recent publications on animal models have investigated the unique antioxidant, anti-inflammatory, spasmolytic, diuretic, and renoprotective effects of "Tutukon®" which is comprised of eight different components (8). As a result of their diuretic, spasmolytic, and anti-inflammatory properties, plant extracts such as those from the Opuntia ficus-indica (9), Rosmarinus officinalis (10), and Cynodon dactylon (11) have been demonstrated to have significant benefits on infection prophylaxis and stone formation (8,24,25).

The goal of this study was to assess the effects of the herbal agent "Tutukon®" on spontaneous passage

rates, time to stone expulsion, and colic attacks during the conservative follow-up of ureteral stones (5-10 mm) without evident blockage or infection. Our data analysis clearly indicated the evident benefits of this agent on these parameters, where a sizeable proportion of patients treated with this therapy passed their calculi in a shorter period of time compared to patients treated with only a conservative medical strategy. There was a decrease in the number of colics observed during weekly follow-up, and in some patients with proximal ureteral stones (who were unable to pass them during 4 weeks of follow-up), the stones migrated from the upper to the lower portion of the ureter, allowing the responsible urologists to more easily and quickly treat them via endoscopic means. Tutukonunique®'s constituents demonstrate the aforementioned various effects (spasmolytic, diuretic, and anti-inflammatory), therefore its administration will aid in expediting the spontaneous passing of ureteric stones in a shorter amount of time before any endoscopic intervention may be necessary.

Increased spontaneous passing rates and decreased colic attacks requiring pain medication are two ways in which "Tutukon®" might improve the quality of life for patients undergoing conservative treatment for ureteral stones (rapid return to daily activities and work, fewer emergency department visits, and fewer surgical procedures). Our previous study addressed the "displacement issue," or the distal migration of proximal ureteral stones during MET treatment. This is a huge plus since it will allow the urologist to do ureteroscopy to remove calculi in a less invasive and risky way. We believe that our findings can help clinicians determine whether or not such herbal drugs are useful in the conservative therapy of ureteral calculi as patients wait for possible spontaneous passage, despite the fact that our trial's small sample size could be a major restriction.

CONCLUSIONS

Our results suggest that patients with medium-sized (10-15 mm) ureteral stones may benefit from the use of the herbal agent "Tutukon®" during the watchful waiting follow-up period to assist and accelerate the spontaneous passage and minimize the number of colic attacks caused by these stones. Additionally distal migration of the stones after Tutukon® application, may maket he subsequent treatment easier and safer.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ethics Committee of Clinica Endourologica Timisoara (Approval number: 02.05.2018/137) The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

All authors contributed equally to this work.

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