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Investigating the Influence of Tutukon and Alfuzosin on Stone Expulsion After Retrograde Intrarenal Surgery

Tutukon ve Alfuzosin'in Retrograd İntrarenal Cerrahi Sonrası Taş Ekspulsiyonu Etkisinin Araştırılması

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ÖZET

Amaç: Retrograd intrarenal cerrahi (RIRC) uygulanan hastalarda bir alfa-bloker (alfuzosin) ile bitkisel bir ajan olan "Tutukon®»un taşsızlık oranları üzerindeki etkilerini karşılaştırmak.

Gereç ve Yöntemler: Ocak 2020 ve Haziran 2020 tarihleri arasında RIRC uygulanan yetmiş beş hasta prospektif olarak değerlendirildi ve retrospektif olarak raporlandı. RIRC sonrası ilaçların taşsızlık oranları üzerindeki etkisini analiz etmek için hastalar üç gruba ayrıldı. Birinci gruba "Tutukon®», ikinci gruba alfuzosin 10 mg ve üçüncü gruba kontrol grubu olarak sadece deksketoprofen reçete edilmiştir. Hastalar ameliyatın dördüncü haftasından sonra taşsızlık oranları açısından tekrar değerlendirildi.

Bulgular: Gruplar (Tutukon®/Alfuzosin/Kontrol) arasında yaş (44.4 ±3.14/43.16 ±2.81/46.00±2.88), taş boyutu, taşın yeri ve ekstrakorporeal şok dalga litotripsi (ESWL) öyküsü açısından fark gözlenmedi (p>0.05). Ameliyat sonrası dördüncü haftada tam taşsızlık oranları; Grup 1 (Tutukon®) %96, grup 2 (alfuzosin) %84 ve grup 3 (kontrol) %76 (p=0.163) olup, Grup 1'deki taşsızlık oranı kontrol grubuna göre anlamlı derecede yüksekti (Grup 1 vs. 3; p= 0.044, Grup 2 vs. 3; p=0.363). Tamamen taşsız hastalar ve klinik olarak önemsiz rezidüel taşları olan hastalar değerlendirildiğinde gruplar arasında fark saptanmadı (p=0.234).

Sonuç: Tutukon® kullanımından elde edilen veriler, alfuzosinin tıbbi eksülsif tedavide kullanımına benzer sonuçlara sahip olup, endoskopik taş cerrahisi sonrası fragman atılmasında tercih edilebilecek bir fitoterapi yöntemi olabileceğini düşündürmektedir.

Anahtar Kelimeler: medikal ekspulsif tedavi, ürolitiyazis, bitkisel ajan, alfa bloker, retrograd intrarenal cerrahi

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ABSTRACT

Objective: To compare the effects of an alpha-blocker (alfuzosin) versus a herbal agent, "Tutukon®,» on stone-free rates in patients who underwent retrograde intrarenal surgery (RIRS).

Material and Methods: We evaluated seventy-five patients who underwent RIRS prospectively consecutively and reported retrospectively between January 2020 and June 2020. Patients were divided into three groups to analyze the effect of medications on stone-free rates after RIRS. "Tutukon®» was prescribed to the first group, alfuzosin 10 mg to the second group, and only dexketoprofen to the third group as the control group. The patients were re-evaluated for stone-free rates after the fourth week of surgery.

Results: Among the groups (Tutukon®/Alfuzosin/Control), no differences were observed in terms of age (44.4±15 .71/43.16±14.05/46.00±14.43), stone size, stone location and extracorporeal shock wave lithotripsy (ESWL) history (p>0.05). Complete stone-free rates at the fourth postoperative week; Group 1 (Tutukon®) was 96%, group 2 (alfuzosin) 84%, and group 3 (control) 76% (p=0.163), and the stone-free rate in Group 1 was significantly higher than that in the control group (Group 1 vs. 3; p= 0.044, Group 2 vs. 3; p=0.363). Evaluation of completely stone-free patients and patients with clinically insignificant residual stones showed no difference between the groups (p=0.234).

Conclusion: The data obtained from the use of Tutukon® have similar results to the use of alfuzosin in medical expulsive therapy, suggesting that it may be a preferred phytotherapy method for fragment expulsion after endoscopic stone surgery.

Keywords: medical expulsive treatment, urolithiasis, herbal agent, alfa blocker, and retrograde intrarenal surgery

INTRODUCTION

Retrograde intrarenal surgery (RIRS) has recently gained popularity for the endoscopic surgical treatment of kidney stones. Despite being a minimally invasive treatment method, RIRS can cause complications such as infection, bleeding, sepsis, and steinstrasse (especially stones > 2 cm) (1). Steinstrasse is seen in 2-10% of patients according to stone size. Twenty-three percent of patients with steinstrasse are asymptomatic, and conservative treatment is the first choice (2).

The aim of the medical treatment of ureteral stones is symptomatic relief, facilitating the passage of stones from the ureter and preventing recurrence. Medical expulsive therapy (MET) increases stone removal rates, decreases the time required for stone removal, reduces the need for analgesic use, and shortens the hospitalization time of patients (3). Additionally, MET is targeted to relax the smooth muscle structure of the ureter without disturbing the ureteral peristalsis, reduce the intensity and frequency of pain felt by the patient, and reduce edema and inflammation in the ureteral mucosa due to stones (4). Researchers have tested various drug options for MET, including nonsteroidal anti-inflammatory drugs, antimuscarinics, phosphodiesterase type-5 inhibitors, steroids, calcium channel blockers, and alfuzosins. Alpha-blockers are the most commonly preferred medical agents (5,6).

The smooth muscle in the distal 1/3 segment of the ureter is known to harbor alpha-1 receptors. Alpha receptor blockage inhibits basal smooth muscle cell tonus and hyperperistaltic wave frequency (6). Various studies have shown that alpha-blockers accelerate stone excretion and facilitate stone passage by causing relaxation of the smooth muscles of the ureteral wall (7,8).

For over two decades, plant-derived terpenes have been employed in ureteral stones medical treatment (9,10). Many patients prefer traditional herbal agents (11,12). Tutukon® is a plant-derived herbal agent that consists of phytosterols, flavonoids, polysaccharides, terpenes, and flavone glycosides. Due to their antioxidant, anti-inflammatory, diuretic, muscle-relaxing, antibacterial, and kidney-protective effects, herbal agents are used in profilaxis of calcium oxalate stones. These herbal agents reduces the excreation of calcium and oxalate in the urine (13).

The current study aimed to compare the effects of alfuzosin versus "Tutukon®" as a herbal agent on stone-free rates in patients who underwent RIRS.

MATERIAL AND METHODS

Study Participants

Data from 75 patients who underwent RIRS between January and June 2020 were collected in a prospective, consecutive manner as part of a systematically designed database. The outcomes were then analyzed and reported retrospectively. Patients were included in the groups in order (1:1:1). Routine hematological and biochemical examinations (serum urea, creatinine, hemoglobin, platelet count, and coagulation tests), urinalysis, and urine culture were performed before surgery. Preoperatively, kidney-ureter-bladder (KUB) and non-contrast abdominal computed tomography (NCCT) were conducted.

Patient age, stone size, stone location, previous stone surgery, and extracorporeal shock wave lithotripsy (ESWL) histories were recorded. This study included patients aged 18 years or above, whose stone size was > 7 mm, with a Hounsfield Unit of 800 or higher, and with visible stones in the KUB, or those with a history of unsuccessful ESWL The study excluded patients who had ureteral stone, were either younger than 18 years or older than 75 years, had elevated levels of urea-creatinine, had a significantly enlarged prostate, reported adverse effects from medication or declined to use medication, had a double-j catheter, had kidney anomalies (e.g. ectopic kidney, horseshoe kidney), had posture disorders, had ureteral stenosis, or had a previous history of stone removal or stone surgery. Patients in whom ureteral access sheath (UAS) could not be placed during surgery were also excluded from the study.

Tutukon® (herbal agent, Laboratorio Miguel&Garriga, S.A. Barcelona, Spain) (3 × 20 ml) was prescribed to the first 25 patients (Group 1) who underwent RIRS as medical expulsive therapy, and alfuzosin (10 mg) was started in the second 25 patients (Group 2). The third 25 patients (Group 3) were included in the study as the control group, and only analgesic treatment (dexketoprofen) was suggested. All patients received existing treatments for four weeks.

Operative Procedure

Two similarly experienced surgeons performed the operative procedures. All operations were performed using a 7.5 Fr fiber-optic flexible ureteroscope (Storz Flex-X2, Tuttlingen, Germany), 9.5/11.5 Fr (Cook, Blooming, USA) UAS and a 0.038-inch hydrophilic guidewire. Standard RIRS was performed under C-arm fluoroscopy in both the groups. Under general anesthesia, following diagnostic ureteroscopy with a rigid ureterorenoscope, dual guidewires were placed into the renal pelvis in lithotomy position. Subsequently, the UAS was placed under fluoroscopy. Stones were fragmented with low power holmium: yttrium–aluminum–garnet (Ho: YAG) laser (200 µm Ho: YAG laser fiber, long pulse 0.4-0.6 J/15-20 Hz for dusting ; short pulse 0.8-1 J/10-15 Hz for fragmentation). Basket catheters were not used for the stone extraction. A 4.8 Fr, 26 cm double J stent was placed in all patients either after the RIRS procedure or in cases where it could not be inserted UAS prior to RIRS. The Double-J stent was removed in the fourth week post-operative.

Evaluation of the Stone Clearance

The KUB, urinary system ultrasonography (US), and NCCT were utilized to evaluate the stone-free rates of patients in the fourth-week post-surgery. Stone clearance was examined using KUB and US in all patients. When residual stone or hydronephrosis was detected by US and KUB, we confirmed the presence of stone by NCCT. Additionally, patients were recorded based on stone-free status and clinically insignificant residual stones. Patients with stones less than 4 mm and without any dilatation, urinary tract infection or pain were considered to have clinically insignificant stones (14).

Statistical Analyses

"SPSS 22 for Windows" was used for statistical calculations. Descriptive statistics for numerical data included mean and standard deviation, while categorical data were expressed as percentages and counts. Normality of the data was assessed using the Shapiro-Wilk test. The chi-square distribution test was used to compare categorical data, and the Mann-Whitney U test was employed for non-normally distributed quantitative data. When comparing more than two groups, the Kruskal-Wallis analysis of variance was utilized. The 95% confidence interval ($p<0.05$) was also considered statistically significant.

RESULTS

When the mean age of the patients in Group 1 (Tutukon®) and Group 2 (alfuzosin) (44.4±15.71 vs. 43.16±14.05) were compared with the control group (Group 3) (46.00±14.43), no significant differences were observed (p=0.771). Similarly, no statistically significant differences were observed between Group 1 (Tutukon®), Group 2 (alfuzosin), and the Group 3 in terms of mean stone size, stone location, and ESWL history **(**respectively p=0.189, p=0.694, p=0.177**) (Table 1).**

Table 1. Comparison of demographic data of patients

	Group 1 (Tutukon), n=25	Group 2 (Alfuzosin), n=25	Group 3 (Control), n=25	p
Age(year) Min-Max Median	44.4 (20-75) 42	43.16 (18-72) 39	 (21-74) 46	0.771
ESWL (n), (%)	6 (24%)	7 (28%)	12 (48%)	0.177
Stone size (mm) Median	 (7-35) 15	 (6-40) 15	 (7-48) 20	0.189
Stone location (n), (%)	pelvis: 19 (76%) multiple calyces: 6 (24%)	pelvis: 18 (72%) multiple calyces : 7 (28%)	pelvis: 21 (84%) multiple calyces : 4 (16%)	0.694

SD: standart deviation, **mm:** milimetres, **n:** number of patients, **ESWL:** Extracorporeal shock wave litotripsy

Complete stone-free rates were 96% in Group 1 (Tutukon®), 84% in Group 2 (alfuzosin), and 76% in Group 3 (control) at the fourth postoperative week (p=0.163) **(Table 2).** When the groups were compared, the stone-free rate in Group 1 was statistically significantly higher than in the control group (Group 1 vs. Group 3; p=0.044). However, there was no statistically significant difference between Group 2 and the control group (Group 2 vs. Group 3; p=0.484).

Three (12%) patients in Group 2 and 3 had clinically insignificant residual stones. When completely stone-free patients and those with clinically insignificant residual stones were evaluated, no difference was observed between the groups (p=0.234) **(Table 2).**

Table 2. Comparison of the stone-free data of the patients

Residue stone	Group1 (Tutukon), n=25	Group2 (Alfuzosin), n=25	Group3 (Control), n=25	p
Completely stone-free (n), (%)	24 (%96)	21 (%84)	19 (%76)	0.163
Clinically insignificant residual stone (n), (%)	0	3 (%12)	3 (%12)	0.234

n: number of patients, **ESWL:** extracorporeal shock wave lithotripsy, mm: millimeters

Postoperative complications were evaluated using the modified Clavien-Dindo classification. Fever requiring postoperative antipyretic treatment was observed in one patient in Group 1 and two in Group 3. No adverse effects were observed due to the use of Tutukon® in Group 1. Two patients in Group 2 experienced hypotension and fatigue due to the use of an alfuzosin; however, no cessation of the medication was necessary, and symptoms regressed after rest and increased fluid intake (p=0.769). Urinary tract infections were detected in one patient in Group 1 and one patient in Group 2 (p=1), and those patients were treated with appropriate antibiotics according to urine culture. Two patients in Group 3 had steinstrasse and needed a re-operation, while the Double-J stent was removing (p=0.324).

DISCUSSION

This study evaluates stone expulsion rates after RIRS with Tutukon®, alfuzosin, and control groups. It is the first study to show the stone expulsion rate with a herbal agent. The Tutukon® group had higher stone expulsion rates than the alfuzosin and control groups. This difference was statistically significant compared to the control group (p=0.044).

Ho: YAG laser is a widely used method for laser lithotripsy. It is considered the gold standard method for lithotripsy because it effectively and safely breaks stones of all compositions and volumes. Considering studies comparing high-power Ho: YAG lasers and low-power lasers in recent years, it has been determined that there is no difference between the stone-free rates, although the operation times and laser usage times are shorter in high-power devices (15,16). In the present study, stones were fragmented using a low-power Ho: YAG laser. The stones were fragmented in dusting mode (dusting setting 0.4-0.6 J/15-20 Hz). A short pulse of 0.8-1 J/10-15 Hz energy was used to fragment hard stones that could not be fragmented in the dusting mode. After the stone fragments were reduced to less than 2 mm, fragmentation was terminated. A basket catheter was not used for stone extraction in any of the patients.

Fragment expulsion after RIRS is critical. Patients and physicians have tried many herbal agents for this purpose owing to their diuretic, antispasmodic, and anti-urolithic effects (9,12). However, precise data on the duration and doses of these agents are yet to be determined. Therefore, our study investigated the effect of "Tutukon®," a herbal agent, on stone-free rates.

Currently, there is no validated protocol or gold-standard method for evaluating residual stones after lithotripsy. NCCT is the gold standard method for demonstrating the presence of residual stones after surgery. However, radiation exposure confuses its use (17). Although approximately 90% of stones are opaque, using KUB alone after lithotripsy is insufficient to show stones less than 2 mm (18). The use of US alone is considered to have lower sensitivity and specificity than NCCT, especially in the absence of hydronephrosis in detecting stones less than 4 mm (19). Catalano et al. compared the combined use of US and KUB with NCCT and showed that the sensitivity of NCCT was higher (92% vs. 77%), as well as the negative predictive value (87% vs. 68%) and overall accuracy (94% vs. 83%) (20). In the present study, we used KUB and US together to determine the post-operative stone-free rates. In cases accompanying hydronephrosis or in patients where residual stones were detected through ultrasound and KUB, the presence of residual stones was confirmed with non-contrast abdominal computed tomography (NCCT).

In a study by Öztürk et al., each physician completed an 11-question form at a relevant clinic to learn about the approaches of 106 urology residents and specialists to ureteral stones. Of the physicians participating in the study, 83% reported using anti-inflammatory analgesics for MET, 90% preferred alpha-blockers, and 5% preferred corticosteroids (21). In a meta-analysis reported by Sharma et al., thirty-one studies were examined. In the study's primary outcome, it was observed that alpha-receptor blockers led to a significant enhancement in the rate of ureteral stone expulsion. Secondary outcome measurements have shown that alpha-receptor blockers increase expulsion of stones, especially those greater than 5 mm, localized in the distal ureter, and shorten the time of stone clearance. This effect has not been demonstrated in stones located in the proximal and middle ureters or those smaller than 5 mm (22). A meta-analysis of randomized controlled studies conducted by Alsaikhan et al. showed that stone-free rates

increased in patients who required ureteroscopy for ureteral stones after alpha-blockers were started preoperatively and continued to be used for four weeks (23).

The concentrations of calcium and oxalate in urine are pivotal factors in the crystallization of stones. Consequently, medications that diminish the urinary excretion of these ions can effectively hinder the genesis and deposition of stone crystals (24). Moreover, alongside the utilization of these pharmaceutical agents, recent findings unequivocally indicate the rising significance of herbal remedies as an efficacious alternative for mitigating the often underestimated toxic effects induced by certain drugs, which may lead to morphological and functional alterations in various organ systems (25). Phytotherapy can be used to ease the toxic effects of these drugs. Research has demonstrated that the majority of phytotherapeutic compounds possess diuretic, anti-inflammatory, antioxidant, vasodilatory, and spasmolytic properties. Essential oils, flavonoids, saponins, xanthine derivatives, and glycosides have been identified as the key active constituents responsible for these specific effects (26,27).

In the study conducted by Yuruk et al., the investigation centered on the impact of Tutukon® on the calcification of zinc disks implanted in the rats bladder. Over a four-week period, they assessed the weights of these zinc disks on days 7, 14, and 28. Their findings indicated that Tutukon® led to a significant reduction in calcification (p=0.275) (28). In the research with rats conducted by Şahin et al.,revealed that Tutukon® administration effectively prevented or mitigated the emergence of apoptotic changes in the renal tubular epithelium, both in the early (14th day) and late (28th day) stages of the study. Moreover, when they evaluated animals given Tutukon® subsequent to the induction of hyperoxaluria, they demonstrated the drug's protective influence on the presence and severity of crystal formation, which was significantly reduced in the Tutukon®-administered group (p=0.031) (29).

A study conducted with some plant extracts in Tutukon® showed that the phytotherapeutic agent used in the patient group treated with endourological methods facilitated the removal of stone fragments and prevented new stone formation (21). Additionally, a review of herbal agents used in patients with kidney disease in Morocco mentioned that Rosmarinus officinalis improves oxonate-induced renal damage in hyperuricemia, and Herniaria hirsuta prevents calcium oxalate and cystine stone formation (30).

No studies have been found in the literature on the use of Tutukon® for MET. In our study, Tutukon® was used for the first time in terms of the kidney stone-free rate, and it was observed that the stone-free rate increased with Tutukon®. Additionally, fragment expulsion after RIRS was higher than in patients without treatment (p=0.047). Although its mechanism of action has not yet been clearly clarified, the data obtained with Tutukon® suggest that it may be a preferred phytotherapy method in medical expulsive treatment and in terms of fragment expulsion after endoscopic stone surgery.

The study's main limitations are the limited sample size and, although not statistically significant, stone size and previous ESWL history differed between groups. Again, although the study was designed prospectively, the fact that it was written in a retrospective nature can be considered another limitation of the study. Despite this, the current study can lead to further studies as a pilot study.

CONCLUSION

In our study, it is believed that Tutukon®, a herbal agent, increased the rates of complete stone clearance after RIRS due to its diuretic and litholytic active metabolities. The main benefit of Tutukon® is that herbal treatment yields similar outcomes to medications. Furthermore, the patient's adherence to the treatment is also improved since it is an herbal agent with minimal side effects.

Conflict of İnterest: The authors have no conflicts of interest to declare.

Statement of Ethics: All procedures involving human participants were performed in accordance with the ethical standards of the Institutional and local Scientific Research ethics committees and with the 1964 Helsinki Declaration. Upon recruitment, each patient provided written informed consent. Ethics committee approval was received for this study from the ethics committee of Gaziantep University (decision no: 2022/249).

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