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ORIGINAL ARTICLE

A review study to evaluate holmium:YAG laser lithotripsy with flexible ureteroscopy in patients on ongoing oral anticoagulant therapy

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Abstract The objective of this study was to evaluate the safety and efficacy of flexible ureteroscopy (FURS) and holmium:YAG laser lithotripsy for the treatment of upper urinary tract stones in patients on active oral anticoagulants. The records of 1081 patients who underwent flexible ureteroscopic holmium:YAG (Ho:YAG) laser lithotripsy for upper ureteral and renal calculi from 1999 to 2015 were retrospectively reviewed. A total of 84 patients on continuous oral anticoagulation or antiplatelet therapy (warfarin, aspirin, or clopidogrel) were identified. Of these patients, 40 were on warfarin, 25 on aspirin, 11 on clopidogrel, and 8 on both aspirin and clopidogrel. The drugs were not discontinued. The baseline characteristics, indications for anticoagulation therapy, perioperative data, stone-free rate, and complications were documented. Evaluation of outcomes was assessed at 1-, 3-, and 6-month follow-up postoperatively. Mean stone size was 19.7 ± 9.4 (range 8 to 31 mm). Twenty patients had upper ureteral and 64 patients had intrarenal calculi. Two patients had bilateral renal calculi. Mean operation time was 78.2 ± 23.8 min (range 17 to 144 min). Two procedures (2.3%) in warfarin group were terminated due to persistent bleeding causing visual impairment. No transfusions were required. The mean serum hemoglobin levels did not change significantly (12.9 ± 3.7 to 12.2 ± 3.3 g/dL). No thromboembolic or cardiac adverse events were observed perioperatively. The double-j (DJ) ureteral catheterization time was 29.6 ± 9.3 days (range 14 to 68 days) and the hospital stay was 1.6 ± 0.6 days (range 1 to 4). The stone-free rate was 95.2% (80 patients) at 6 months. Flexible ureteroscopic Ho:YAG laser lithotripsy in patients requiring long-term anticoagulation therapy seems to be a safe and effective procedure and should be considered as a first-line treatment option in such patients for the surgical management of upper urinary tract stones.

Keywords Flexible ureteroscopy · Ho:YAG laser · Oral anticoagulants · Kidney stone

Introduction

The number of patients requiring oral anticoagulation is steadily growing, and thus, more patients requiring surgical treatment for urinary stone disease are on oral anticoagulation therapy (OAT). Aspirin (acetylsalicylic acid) and vitamin K-dependent antagonists, such as warfarin, are the most commonly prescribed drugs worldwide and significantly reduce the risk of thrombotic events at the cost of increased risk of bleeding. Stone disease in patients on chronic OAT poses a challenging management problem. Anticoagulation medication is a strict contraindication to the extracorporeal shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL), laparoscopic and open surgery with regard to bleeding complications. However, interruption of OAT for surgery increases the risk of thromboembolism and cardiac adverse events. Thus, the use of flexible ureterorenoscopes (FURS) and laser lithotripsy may be the only feasible surgical option in such case, providing a minimally invasive definitive treatment.

The most common lasers used for lithotripsy are as follows: pulsed dye lasers (595 nm), alexandrite lasers (750 nm), frequency-doubled double-pulse neodymium:YAG (FREDDY) lasers (532/1064 nm), and holmium:YAG

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(Ho:YAG) lasers (2100 nm) [1]. Ho:YAG laser is usually utilized with a pulse length (duration of each pulse of laser energy) of 500 μs. Smaller stone fragments can be produced by using Ho:YAG laser when compared with other pulsed lasers [2]. Moreover, since Ho:YAG laser energy is absorbed by all stone compositions, this laser can be used to fragment all stone types, including the harder cystine and calcium oxalate monohydrate calculi [2, 3].

In patients with bleeding diatheses, only a few studies on the surgical treatment by Ho:YAG laser lithotripsy for upper tract calculi have been published and promising midterm results were demonstrated [4–6]. Literature evaluating the limitations of FURS and laser lithotripsy in patients taking OAT has been quite sparse to date. Only one study by Turna et al. reported a retrospective comparative study specifically addressing the surgical treatment of 37 patients on ongoing oral anticoagulants (aspirin, warfarin, and clopidogrel) by flexible ureteroscopic laser lithotripsy and showed that FURS is a safe procedure, with good early clinical outcomes [7].

The purpose of the current study was to evaluate the safety and clinical efficacy of the flexible ureteroscopic Ho:YAG laser lithotripsy in patients on ongoing OAT. To our knowledge, this is the largest reported experience of Ho:YAG laser lithotripsy with FURS outcomes in patients on active oral anticoagulation to date.

Patients and methods

With Institutional Review Board approval, the records of 84 patients receiving oral anticoagulants (warfarin, aspirin, and clopidogrel) who were treated with flexible ureteroscopic Ho:YAG laser lithotripsy for upper ureteral and intrarenal stones at Medipol University Hospital between March 1999 and January 2015 were retrospectively reviewed. OAT involved warfarin in 40 patients (47.6%), aspirin in 25 (29.7%), clopidogrel in 11 (13%), and both aspirin and clopidogrel in 8 (9.5%). The mean duration of anticoagulation at surgery was 19.7 months (range 2 to 79). There was no perioperative discontinuation in drug administration since withdrawal would have posed a significant risk for thromboembolism. The reasons for chronic OAT, doses of the drugs, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) values were recorded. Table 1 lists the main reasons for chronic OAT.

Clinical parameters, including the American Society of Anesthesiologists (ASA) score, stone size and location, operative time, perioperative bleeding causing visual impairment, length of hospitalization, postoperative persistent macroscopic hematuria, readmission due to bleeding, changes in preoperative and postoperative hemoglobin levels, stone-free status, early and late postoperative bleeding or thrombotic complications, and the overall transfusion rate, were documented.

All patients underwent noncontrast CT before surgery. All procedures were performed by using our previously described technique [8] by using five different flexible ureterorenoscopes (Flex-X, Flex-X2, and Flex-XC, Karl Storz, Tuttlingen, Germany; and URF-P3 and URF-P5 Olympus Surgical, Orangeburg, NY). Ho:YAG laser fibers (StoneLight, AMS, MN, USA and Spinx, LISA, Katlenburg-Lindau, Germany) of varying sizes (150, 200, or 272 μm) which were used as a lithotripter. In all patients with upper ureteral calculi, we pushed the stone back to the renal pelvis before fragmentation. Laser fragmentation was performed in the renal pelvis after this "push-back" maneuver. The laser energy levels and pulse frequencies were 0.6–1.0 J and 5–10 Hz, respectively. Stone extraction was not performed in any cases to reduce operative time and mucosal injury. A double-j (DJ) ureteral stent of varying sizes (4.8–6.0 Fr) was placed routinely. Postoperative first day patients were discharged if the urine was clear and the patient was stable. A second-generation oral cephalosporin was given to all patients postoperatively for 1 week.

All patients were evaluated at 1-month follow-up visit with coagulation parameters, hemoglobin levels, renal ultrasound, kidney-ureter-bladder (KUB) X-ray, and CT if necessary. Stone-free status was assessed at this point. Residual fragments >2 mm were considered treatment failure. Patients with residual fragments were evaluated at 3- and 6-month follow-up visits. All patients were counseled and written consents were received from them all. The ethics committee of our university hospital approved the protocol.

All data are presented as a mean ± standard deviation (SD) or the number of available cases (percentage). Statistical analysis of the patients' baseline characteristics was performed using the Student *t* test. To compare preoperative and postoperative clinical parameters, paired *t* test or analysis of variance was used. Statistical analysis was performed using the SPSS 15.0 (SPSS Inc., Chicago, IL) statistical software package. A p value of less than 0.05 was considered statistically significant.

Results

Mean age of overall cohort was 70.8 ± 9.8 years (range 47 to 90). Mean ASA classification was 2.7 ± 0.5 (1–4). The mean stone size was 19.7 ± 9.4 mm (8 to 31 mm) with a mean operating time of 78.2 ± 23.8 min (17 to 144 min). Mean laser energy level, pulse frequency, and total energy required for complete fragmentation were 0.9 ± 0.1 J (range 5 to 10), 7.9 ± 1.9 Hz (range 5 to 10), and 5.7 ± 1.9 kJ (range 0.6 to 18.1), respectively. A 15-Fr ureteral dilating balloon was used in 2 patients (2.3%). Ureteral access sheath was used routinely except in 2 patients in the aspirin group and 1 patient in the clopidogrel group. Double-J ureteral stent placement was performed routinely at the end of the procedure. Mean DJ ureteral stent removal time and mean hospital stay were 29.6 ± 9.3 days

Table 1 Indications for oral anticoagulation therapy (OAT)

	Warfarin (n = 40)	Aspirin (n = 25)	Clopidogrel (n = 11)	Aspirin + clopidogrel (n = 8)
Chronic atrial fibrillation	18	0	0	0
Cerebrovascular disease	6	4	2	1
Coronary heart disease	2	14	5	3
Prosthetic heart valve	7	2	1	1
Deep venous thrombosis	6	0	0	0
Peripheral arterial disease	0	5	3	3
Pulmonary embolism	1	0	0	0

(range 14 to 68) and 1.6 ± 0.6 days (range 1 to 4), respectively. Overall stone-free rates at 1 and 6 months postoperatively were 91.6% (77 patients) and 95.2% (80 patients), respectively. The mean initial stone size of the seven patients which were not stone-free at 1 month was 24.7 ± 9.1 (range 19 to 31). Perioperative parameters of each group are listed in Table 2.

Intraoperative and postoperative adverse events of each group are shown in Table 3. The procedure was discontinued in 2 patients (2.3%) with impaired visibility due to uncontrolled bleeding during laser fragmentation in the warfarin group. Renal pelvic injury in one patient (1.1%) in the aspirin group and upper ureteral injury in 1 patient (1.1%) in clopidogrel group were observed at the end of the procedures and both were managed with prolonged ureteral catheterization successfully. No blood transfusions were required, and no thromboembolic or cardiac adverse events were observed. Mean serum hemoglobin levels did not change significantly (12.9 ± 3.7 vs 12.2 ± 3.3). Bladder irrigation with saline was required only in 1 patient (1.1%) in the warfarin group due to persistent hematuria. Transient macroscopic hematuria was observed in 5 patients (12.5%) in warfarin, 4 patients (16%) in aspirin, and 2 patients in aspirin + clopidogrel group early postoperatively. Late hematuria was not observed in any groups. High fever with positive blood culture was noted postoperatively in 1 patient (1.1%) and a third-generation intravenous cephalosporin was administered for 3 days. Urinary tract infections (UTIs) were seen in 3 (3.5%), 0 (0%), 1 (1.1%), and 1 (1.1%) patients in the warfarin, aspirin, clopidogrel, and aspirin + clopidogrel groups within 1 month, respectively. Ureteral stricture was not observed in any patient. Overall, based on the Clavien-Dindo classification of adverse events, 11 patients (13%) had grade I complications, while 2 patients (2.3%) had grade II and 2 patients (2.3%) had grade III-b complications.

Discussion

Antithrombotic agents have been developed to inhibit platelets or coagulation factors. The initial oral antiplatelet and oral anticoagulant treatments successfully reduce thrombotic events. Acetylsalicylic acid (aspirin) is the most prescribed antiplatelet agent for prevention of cardiovascular adverse events. Low doses of aspirin selectively inhibit cyclooxygenase (COX)-1, resulting in antiplatelet effects [9]. Vitamin K-dependent antagonists (VKAs), such as warfarin, are the most commonly prescribed oral anticoagulants. By antagonizing vitamin K, warfarin disrupts the formation of clotting proteins dependent on vitamin K, including factors II, VII, IX, and X, and proteins C and S. Warfarin has a mean plasma half-life of 40 h and the complete anticoagulant effects emerge 48–72 h after its

Table 2 Perioperative parameters of patients on ongoing oral anticoagulation therapy (OAT)

	Warfarin (n = 40)	Aspirin (n = 25)	Clopidogrel (n = 11)	Aspirin + clopidogrel (n = 8)
Mean age	72.8 ± 8.9	69.5 ± 7.7	68.3 ± 9.1	69.1 ± 8.4
ASA	2.6 ± 0.3	2.7 ± 0.2	2.6 ± 0.6	2.7 ± 0.4
Stone size (mm)	16.6 ± 8.1	17.9 ± 4.8	20.1 ± 4.7	19.1 ± 9.9
INR	2.6 ± 0.7	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.2
Operation time (min)	81.4 ± 32.9	75.1 ± 28.1	76.3 ± 31.7	75.5 ± 29.6
Applied energy (kJ)	5.1 ± 1.9	5.9 ± 1.7	6.9 ± 1.8	6.7 ± 2.1
Hospitalization (days)	1.6 ± 0.5	1.5 ± 0.3	1.6 ± 0.4	1.7 ± 0.9
Catheter removal time (days)	28.9 ± 8.5	29.9 ± 7.1	26.6 ± 9.8	31.9 ± 8.9
Stone-free rate at 1 month	90% (n = 36)	88% (n = 22)	100% (n = 11)	100% (n = 8)

ASA American Society of Anesthesiologists score, *INR* international normalized ratio

Table 3 Intraoperative and postoperative adverse events of patients on ongoing oral anticoagulation therapy (OAT)

	Warfarin (n = 40)	Aspirin (n = 25)	Clopidogrel (n = 11)	Aspirin + clopidogrel (n = 8)
Intraoperative bleeding causing visual impairment	2	0	0	0
Ureteral or renal pelvic injury	0	1	1	0
Postoperative persistent macroscopic hematuria	1	0	0	0
Transfusion	0	0	0	0
Readmission due to bleeding	0	0	0	0
Urinary tract infection	3	0	1	1
Thromboembolic event	0	0	0	0

administration. Bleeding complications with warfarin are one of the main causes of severe adverse drug events. Administration of vitamin K or infusion of clotting factors must be used in such conditions for reversal of anticoagulant effects [10]. But it should not be forgotten that sudden discontinuation of warfarin and vitamin K infusion for hemostasis in a bleeding patient can also lead to massive intravenous thrombosis such as deep venous thrombosis (DVT) or renal vein thrombosis.

Particularly in patients with large kidney stones, PNL has a major advantage that the stone fragments can be removed. However, this technique is so risky in patients on ongoing OAT. Open surgery, PNL, laparoscopy, and SWL are all considered strictly contraindicated in patients with uncorrected bleeding diathesis due to the high risk of significant blood loss. Therefore, discontinuing the antiplatelet agents 3–7 days before the surgery and re-initiating early postoperatively or bridging therapy in patients taking warfarin (temporary use of parenteral low molecular weight heparin) have been the most common practices to date. However, many studies reported that discontinuing the OAT in patients with atrial fibrillation, high risk of DVT or high risk for cardiovascular diseases (previous angina, stroke, or transient ischemic attack) can increase the risk of stroke, DVT, life-threatening thromboembolic events, and acute coronary syndrome [11–13]. Therefore, FURS with laser lithotripsy seems to be the most favorable surgical treatment option in patients on ongoing chronic OAT [14, 15]. holmium:YAG laser is versatile in fragmenting stones of all compositions, including cystine and calcium oxalate monohydrate [16]. In addition, the holmium:YAG laser has hemostatic properties that would be beneficial in patients with bleeding diathesis [17]. Holmium laser energy is rapidly absorbed by saline due to its unique wave length of 2100 nm. The risk of perforation is very low if the distance between the ureter and the fiber tip is more than 1 mm [18].

Kuo et al. first reported the efficacy and safety of holmium laser lithotripsy by using both semirigid and flexible ureteroscopes in 7 patients with bleeding diatheses (5 receiving coumadin, 1 thrombocytopenic, and 1 von Willebrand disease) in 1998 [4]. They reported only one postoperative bleeding complication and stone-free rate of 85.7% at 1 month. In a larger cohort of 25 patients (17 receiving coumadin, 3 with liver dysfunction, 4 with thrombocytopenia, and 1 with von Willebrand disease), Watterson et al. reported a 96% stone-free rate [5]. Significant retroperitoneal hemorrhage requiring transfusion in 1 patient who was treated concomitantly with electrohydraulic lithotripsy was also reported. Thus, they concluded that avoiding electrohydraulic lithotripsy is crucial for preventing serious bleeding complications. The high peak pressures generated by electrohydraulic lithotripsy may be transmitted beyond the ureter, potentially resulting in significant bleeding. Therefore, they emphasized that the holmium laser must be the only modality of lithotripsy.

In a recent study by Turna et al., the use of FURS with laser lithotripsy for the treatment of renal calculi was retrospectively reviewed in 37 patients on OAT and compared with a matched control group [7]. Although the anticoagulated patients were older, and with higher ASA scores, all procedures were completed without any complication and both groups had similar stone-free rates. Importantly, no transfusions or significant drop in hemoglobin was observed. They emphasized that FURS is safe and effective in these patients and in experienced hands.

In this study, we also aimed to evaluate the efficacy and safety of the use of FURS with laser lithotripsy for the treatment of upper ureteral and renal stones. To the best of our knowledge, this is the largest reported experience of the combination of Ho:YAG laser lithotripsy and FURS in patients on active oral anticoagulation to date. Our results revealed that favorable stone-free rate (95.2%) with minimal hemorrhagic adverse events (3.5%) can be achieved by using holmium:YAG laser and FURS combination in patients with upper urinary tract stones. Our usual technique was employed with minor changes. In particular, stone extraction was not performed in any cases and a DJ ureteral stent was placed routinely. In our clinical experience, routine DJ ureteral stent placement significantly reduces the renal colic episodes, the postoperative flank pain, and the rate of pyelonephritis secondary to ureteral obstruction. In our study, residual fragments >2 mm were considered treatment failure because the spontaneous ureteric stone passage rate for fragments <2 mm is reported >95% [19]. Flexible ureteroscopy and Ho:YAG laser provides a very controlled stone fragmentation when

compared with SWL and electrohydraulic lithotripter. It is quite easy to obtain very small (<1–2 mm) and homogeneous multiple fragments by using Ho:YAG laser. In this cohort, stone extraction was not performed in any cases in order to reduce the operative time, mucosal injury, and complications. Moreover, our surgical technique using the holmium:YAG laser focused on making quite small (<1–2 mm) fragments. Thus, stone extraction was not needed in any cases. Both FURS and SWL are the most preferred options for the management of residual stones after PNL. Chen L et al. investigated the effectiveness of FURS and holmium laser lithotripsy for the treatment of residual stones after management of complex calculi with single-tract PNL and reported a stone-free rate of 88.9% [20]. However, we could not find any previous research comparing FURS and SWL in these patients.

In this cohort, only two procedures (2.3%) were discontinued due to persistent bleeding and impaired visibility in the warfarin group. No transfusions were required. In addition, there were no significant events related to anticoagulation late postoperatively. Our data, in terms of stone-free rate and complications, were similar to the previously reported studies with the similar technique in patients with various bleeding disorders [4–6]. The major limitation of the present study is the lack of a control group in the study design. A randomized controlled trial with long-term follow-up should provide better evidence in this regard.

Conclusions

Holmium:YAG laser lithotripsy using small caliber flexible ureterorenoscopes represents a novel option for the urologists in the management of upper tract urinary calculi in patients with bleeding diatheses. Our initial experience with the combination of FURS and holmium:YAG laser indicates that the technique is an excellent choice for the treatment of upper urinary tract stones in patients on ongoing oral anticoagulant therapy. Further randomized, prospective, and controlled studies with larger number of patients should be designed to investigate the effectiveness and safety of treating residual stones with FURS and holmium laser lithotripsy after managing complex calculi with single-tract PNL. Patients with other bleeding disorders can also be successfully treated with no increased risk of hemorrhagic adverse events with this technique. Our results suggest that holmium:YAG laser lithotripsy with flexible ureteroscopy in these patients should be considered as a first-line treatment option. However, a future comparative study would be nice to assess this issue.

Compliance with ethical standards All patients were counseled and written consents were received from them all. The ethics committee of our university hospital approved the protocol.

Conflict of interest The authors declare that they have no conflict of interest.

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