Retrograde Intrarenal Surgery following Laser Endopyelotomy; Sequential Procedures for Ureteropelvic Junction Obstruction and Nephrolithiasis

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Purpose: This study was designed to evaluate the effectiveness and safety of retrograde intrarenal surgery (RIRS) following retrograde laser endopyelotomy (rLEP) in concomitant ureteropelvic junction obstruction (UPJO) and stone disease.

Materials and Methods: Patients with concomitant UPJO and renal stone disease who were first treated in our clinic by rLEP for obstruction and then RIRS for stone disease were enrolled. Study period went from 2012 to 2017. RIRS following rLEP was performed earliest at the sixth week. Patients who underwent rLEP were matched with those with normal anatomy at a 1:1 ratio based on the propensity scores. Additionally, clinical results were compared in order to evaluate the effects of rLEP surgery on RIRS. Subsequently, patients who underwent RIRS following rLEP were independently evaluated and factors affecting the success of sequential procedures were investigated.

Results: The sole difference between those that underwent RIRS following rLEP (n=27) and controls with normal anatomy that underwent RIRS was in operative times (p = .011). Evaluation of potential success factors in the sequential rLEP-RIRS group revealed that primary etiology, obstruction length less than 1cm, smaller stone size and presence of single stone showed significant effects (p = .047, p = .030, p = .040, $p \leq$ .001, respectively). RIRS following rLEP generated an 81.5% stone-free and, after a median follow-up time of 32 months, a 74.1% obstruction-free rate.

Conclusion: RIRS following rLEP in patients with UPJO and renal stones is an effective treatment method. It can be used safely in patients with single stones < 2cm, short obstruction lengths, and presence of primary etiology.

Keywords: endopyelotomy; retrograde intrarenal surgery; sequential; stone; ureteropelvic junction obstruction

INTRODUCTION

Patients with ureteropelvic junction obstruction (UPJO) have been reported to develop concomitant ipsilateral renal stone disease at rates of approximately 20.0%.[1,2] In UPJO patients, urinary stasis, metabolic anomalies and infection are predisposing factors for stone formation.[3,4]

Reduced recurrence of renal stone disease following UPJO treatment further corroborates the pathophysiology.[5] It has been previously shown that UPJO and renal stones can be treated with alternatives to open surgery. Specifically, studies have established percutaneous access, antegrade endopyelotomy performed with nephrolithotomy, and stone removal simultaneously with laparoscopic or robotic pyeloplasty. While these methods are minimally-invasive, some of these techniques are associated with disadvantages such as the opening of the peritoneum, risk of intestinal injury, proximity to major arteries, long operative times, and difficult techniques.[6] Therefore, at this time, investigations for alternative treatments is still ongoing.

The present study was conducted to evaluate the retrograde intrarenal surgery (RIRS) following retrograde laser endopyelotomy (rLEP). Specifically, this approach could constitute an additional effective and safe minimally-invasive method for patients with concomitant UPJO and stone disease.

MATERIALS AND METHODS

In the present retrospective study, patients with UPJO and ipsilateral renal stone who underwent RIRS following rLEP in our clinic between January 2012 and June 2017 were evaluated. Ethical committee approval was obtained prior to study commencement.

Exclusion criteria were as follows; obstruction greater than 2cm, tumor on the side of the obstruction, suspected obstruction related to the crossing vein, extrinsic ureteral obstruction, ureteral high insertion, ipsilateral

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Table 1. Perioperative characteristics of RIRS in control and case groups.

	Control group (n=27)	RIRS following rLEP (Case group) (n=27)	*p*-value
Age	40.4 ± 14.1	39.6 ± 10.6	0.828[a]
Gender			0.577[b]
Male	9 (33.3%)	12 (44.4%)	
Female	18 (66.7%)	15 (55.6%)	
Side			-
Right	13 (48.1%)	13 (48.1%)	
Left	14 (51.9%)	14 (51.9%)	
BMI (kg/m^2)	24.8 ± 3.3	25.9 ± 4.1	0.262[a]
ASA score			0.744[c]
I	11(40.7%)	13 (48.1%)	
II	14 (51.9%)	11 (40.7%)	
III	2 (7.4%)	3 (11.2%)	
Stone Size (mm)	13.3 ± 6.82	15.5 ± 2.79	0.126[a]
Number of Stones	1 (1–6)	1 (1–4)	0.667[c]
Single	19 (70.4%)	17 (63.0%)	0.773[b]
Multiple	8 (29.6%)	10 (37.0%)	
Stone Localization			0.865[b]
Lower pole	14 (51.9%)	11 (40.7%)	
Pelvis	6 (22.2%)	8 (29.6%)	
Middle and Upper pole	2 (7.4%)	2 (7.4%)	
Multiple Calyxes	5 (18.5%)	6 (22.2%)	
Ureteral access sheath			0.080[b]
Not used	2 (7.4%)	8 (29.6%)	
Used	25 (92.6%)	19 (70.4%)	
Operative time (min)	45 (15–80)	55 (30–80)	0.011[c]
Stone-free state (Success)	25 (%92.6)	22 (%81.5)	0.420[d]
Hospitalization (days)	1 (1–2)	1 (1–7)	0.078[c]
Complications	1 (3.7%)	3 (11.1%)	0.610[d]

Abbreviations: a: Student's *t* test, b:Chi-square test, c: Mann Whitney U test, d: Fisher's exact test.

renal function (IRF) percentage below 20% and patients under the age of 18. Furthermore, patients who, by preoperative imaging, demonstrated impacted stone in the UPJ and whose stone was in contact with UPJ were excluded from the study. Such decision was based on the grounds that in these patients an obstruction might form in the ureteropelvic junction due to edema. Also, since guidelines generally recommend RIRS procedure for stones < 2cm, 4/31 patients were excluded, leaving 27 patients to be evaluated. Excluded patients were referred to other treatment modalities.

In order to rule out the UPJO related to the stone's potential impact and to determine the obstruction's location and length, the rLEP process was initiated with retrograde pyelogram. Additionally, the obstructing ureteral segment's length was assessed by endoscopy under direct vision. Subsequently, upon visualizing UPJ with semirigid or flexible ureteroscopy, it was clarified that the obstruction didn't develop secondary to the stone. As a consequence, the process was continued. Pulsations at the stricture area were also evaluated. A semirigid ureteroscope (Karl Storz, Tuttlingen, Germany) with an 8-Fr tip, 9.5-Fr shaft, and a 7.5-Fr flexible ureteroscope (Flex X2; Karl Storz, Tuttlingen, Germany) was used. A 365-µ laser fiber was used with the semirigid ureteroscope, and a 200-µ laser fiber was used in the flexible ureteroscope. A posterolateral or lateral incision was performed under direct vision. To this end a Ho:YAG laser with an energy of 1.5–2.5 J and a frequency of 10–15 Hz was used. Appropriate incision depth was confirmed by direct vision and by documenting contrast extravasation. No complication such as extravasation of the stone which would have constituted an impediment to perform RIRS following rLEP.

All patients were taken under operation planned to undergo RIRS at a median of 6 weeks (6–10 weeks). Of note, it was kept in mind the possibility of a dilatation effect of the stent after rLEP, coverage of the incised area by the urothelium after 5 days from the urethral incision, and muscular regeneration taking place in 6 weeks.[8] In order to evaluate extravasation and obstruction, RIRS following rLEP was commenced with retrograde pyelogram. In a subset of patients for whom the pyelogram did not suggest the presence of leakage and abnormal ureteropelvic junction image, a ureteral access sheet (UAS) was placed under the control of the scope, taking care not to advance to the UPJ. Ureteral stents of those patients with no complication and not recommended for additional treatment at the end of the first month after RIRS, were removed under local anesthesia.

Patients who were to undergo rLEP were evaluated by computed tomography (CT) and dynamic nuclear scintigraphy. Stone size was calculated as the longest diameter of the stone measured by CT. For multiple stones, diameter was evaluated as the sum of the maximum diameter of the stones. Preoperative and postoperative UPJO was accepted as follows: radiological absence of drainage, presence of obstructive pattern in the clearance curve by dynamic scintigraphy, and T1/2 being > 20 minutes. Treatment success was defined as the absence of diagnostic criteria for UPJO, signs of symptoms' regression, preservation of renal function, complete absence of stones, and residue < 3 mm that doesn't require surgery. Postoperative patient follow-up occurred at the 1st, 3rd, 6th, and 12th month and thereafter annually, with the goal of evaluating surgical success. At the end of the 3rd month, patients were checked by CT and dynamic nuclear scintigraphy. These investigations were repeated in cases of suspicion of obstruction's recurrence. Patients' characteristics, obstruction

Table 2. Demographic and clinical characteristics of cases with successful and unsuccessful outcomes following sequential rLEP and RIRS treatment.

	Unsuccessful (n=5)	Successful (n=22)	*p*-value
Age	37.0 ± 9.2	40.2 ± 11.1	0.551[a]
Gender			0.628[b]
Male	3 (60.0%)	9 (40.9%)	
Female	2 (40.0%)	13 (59.1%)	
Side			0.648[b]
Right	3 (60.0%)	10 (45.5%)	
Left	2 (40.0%)	12 (54.5%)	
BMI (kg/m^2)	26.2 ± 2.1	25.9 ± 4.4	0.873[a]
ASA score	1 (1–2)	2 (1–3)	0.524[c]
Etiology			0.047[b]
Primary	1 (20.0%)	16 (72.7%)	
Secondary	4 (80.0%)	6 (27.3%)	
Preoperative hydronephrosis			0.621[b]
Grade 2	1 (20.0%)	9 (40.9%)	
Grade 3	4 (80.0%)	13 (59.1%)	
Incision site			0.616[b]
Posterolateral	3 (60.0%)	16 (72.7%)	
Lateral	2 (40.0%)	6 (27.3%)	
Obstruction length			0.030[b]
<1cm	1 (20.0%)	17 (77.3%)	
≥1cm	4 (80.0%)	5 (22.7%)	
Ipsilateral renal function			0.079[b]
<30%	2 (40.0%)	1 (4.5%)	
≥30%	3 (60.0%)	21 (95.5%)	
Stone Size (mm)	17.8 ± 1.48	15.0 ± 2.78	0.040[a]
Number of Stones	2 (2–4)	1 (1–2)	< 0.001[c]
Multiple stones	5 (100.0%)	5 (22.7%)	0.003[b]
Stone Localization			0.295[d]
Lower pole	3 (60.0%)	8 (36.4%)	
Pelvis	-	8 (36.4%)	
Middle and Upper pole	-	2 (9.1%)	
Multiple Calyxes	2 (40.0%)	4 (18.2%)	
Ureteral access sheath			> 0.999[b]
Not used	1 (20.0%)	7 (31.8%)	
Used	4 (80.0%)	15 (68.2%)	
Time between rLEP and RIRS	7 (6–9)	6 (6–10)	0.650[c]

Abbreviations: BMI: Body mass index, ASA: American Society of Anesthesiologists score, rLEP: Retrograde laser endopyelotomy, RIRS: Retrograde intrarenal surgery, a: Student's t test, b: Fisher's exact test, c: Mann Whitney U test, d: Pearson's Chi-square test.

and stone's effects on treatment success were investigated. Complications were classified according to the Clavien-Dindo classification.

Stricture site and length were obtained from the operative notes, as well as the preoperative and intraoperative radiographic studies. Evaluation for crossing vessels was performed by CT and by observing pulsations at the stricture area during ureteroscopy. Patients with suspicion of polar vessels were excluded.

Primary UPJO was accepted to be of congenital origin and due to functional obstruction without previous renal surgery. Secondary etiology was acquired, and linked to a history of surgery in UPJ, stones in the UPJ and failed treatment for UPJO. Preoperative hydronephrosis was evaluated radiologically prior to rLEP as grade 2 (moderate) and grade 3 (severe). In the dynamic nuclear scintigraphy performed before rLEP, evaluation was made according to IRF's percentage, as below and above 30.

Stone characteristics were considered to have impact on clinical outcomes. Additionally, other factors that play such a role, including: age, gender, side, body mass index (BMI), and American Society of Anesthesiologists (ASA) score. As a consequence, such factors were included in the multivariate logistic regression model and propensity scores of patient groups with normal anatomy who underwent RIRS (control) and patient groups who underwent RIRS following rLEP (case). According to the probability estimations obtained from logistic regression analysis with 27 cases, 27 of the 1229 control cases were matched. Two groups were compared in terms of operative and postoperative features.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics software version 17.0 (IBM Corporation, Armonk, NY, USA). The assumptions of normality and variance homogeneity were examined by Kolmogorov-Smirnov and Levene test, respectively. Continuous variables were shown as mean ± SD or median (min-max) where applicable.

Propensity scores were obtained by using a multiple logistic regression model where the dependent variable indicated whether the patient was sequential rLEP and RIRS (= 1) or with normal anatomy (= 0). Propensity scores estimated the probability of sequential rLEP and RIRS or with normal anatomy, given the covariates in the model. Independent covariates were as follows: age, gender, localization, BMI, ASA, duration of operation, status of success and hospitalization. Patients were matched 1:1, which randomly selects a case and matches them to the nearest control subject.

The mean differences between groups were compared using the Student's t-test. Additionally, the Mann Whitney U test was applied for comparison of data with non-normal distribution. Categorical data were analyzed by Pearson's Chi-square, Continuity corrected

Table 3. Minimally-invasive series with over 10 patients that report on the treatments used in cases of concomitant UPJO and renal stones providing stone-free and obstruction-free rates.

	Technique	Number of Patients	Stone Size (mm)	Operative Time (min)	Hospitalization Time (days)	Complications(%)	Stone free %	Obstruction-free (%)	Follow-up (months)
Inagaki(7)	Laparoscopy	21	-	-	-	-	98	100	24
Stein(8)	Laparoscopy	15	5.8	174	1.6	6.7	93	80	5.4
Stravodimos(11)	Laparoscopy	13	8.7	218	4	2	84.6	100	30.2
Ramakumar(12)	Laparoscopy	20	1.4 cm^2	276	3.4	0	90	90	12
Srivastava(13)	Laparoscopy	20	15	168	4.9	15	75	90	34
Mufarrij(9)	Robotic	13	-	235	2	0	100	100	28.5
Nayyar(10)	Robotic	10	-	-	-	-	80	100	-
Berkman(14)	Endo-pyelotomy+PNL	41	-	-	-	-	90	90	29
Agarwal(15)	Laparo-scopy+PNL	10	3–24	234	5.2	20	100	100	6
Current Sequential	rLEP+ RIRS	27	15.5	107.1	4.0	11.1	81.5	74.1	32

Abbreviations: PNL=Percutaneous nephrolithotomy, rLEP=Retrograde laser endopyelotomy, RIRS=Retrograde intrarenal surgery.

Chi-square or Fisher's exact test, where applicable. A *p*-value < 0.05 was considered statistically significant.

RESULTS

As described in **Table 1**, when comparing the RIRS procedure following rLEP vs. control groups, no differences were found in terms of preoperative demographic data (age, gender, side, BMI, ASA score, stone size, number of stones, and stone localization). Regarding the perioperative data, median operative time was significantly higher for the case vs. the control group ($p = .011$). Retrograde LEP's operative time, which is naturally only in case group, was calculated as median 52 (36-75) minutes.

In patients who underwent RIRS following rLEP, factors that could affect the overall success of combined sequential therapy were evaluated. Having primary etiological origin, an obstruction length < 1cm, the small stone's size and the small stone's number were found to be statistically significant ($p = .047$, $p = .030$, $p = .040$, $p < .001$, respectively).

At the end of 3 months, 22 patients (81.0%) achieved stone-free states and success in UPJO treatment. Although a stone-free state was achieved, one patient manifested symptoms at month 6 and another at year 1. Specifically, patients developed obstructive patterns in dynamic scintigraphy that were performed subsequently, amounting to an overall success rate of 74.1% over a median follow-up time of 32 (14–72) months.

One patient was referred to another treatment modality due to obstruction continuing in the retrograde pyelogram and the inability to pass the flexible ureteroscope. In this patient, treatment was considered as failure. In absence of leakage suspicion and of an abnormal ureteropelvic junction image on the pyelogram, the UAS was placed in 17 patients under the control of the scope, taking care not to advance to the UPJ.

DISCUSSION

When UPJO and stones are detected, active treatment is needed in order to reduce stone recurrence.[3] Percutaneous nephrolithotomy (PNL) is the most prominent choice for patients with anatomical anomalies and high stone burdens. However, the optimum treatment option for concomitant UPJO and stones, remains unclear to date.

Earlier studies have shown that cases of renal stones and UPJO can be safely and effectively treated by endourological surgery (**Table 3**).[7-15] Of note, studies on laparoscopic and robotic pyeloplasty for the simultaneous stone removal usually include limited numbers of patients. In their non-systematic review, Skolaris et al. reported mean stone-free rates of 91.3 and 92.3%, obstruction-free rates of 96.1 and 100%, and long operative times of 3.45 and 4.21 hours for of simultaneous laparoscopic and robotic pyeloplasty, respectively.[6]) Considering the technical difficulty of laparoscopic and robotic pyeloplasty, RIRS performed subsequently to rLEP possesses serious advantages (e.g., ease of application and short operative times). Of note, robotic pyeloplasty's lack of tactile sensation and high costs should be kept in mind. Finally, another advantage of endopyelotomy is that high success rates can be achieved with other treatment modalities following a failed endopyelotomy.[16]

Studies have investigated the combined use of simultaneous endourological operations (e.g., laparoscopy with PNL). However, these treatment methods have disadvantages.[15] Specifically, the irrigation fluid may accumulate between intestinal loops, giving rise to metabolic effects. Additionally, stone localization in the obstructed calyxes is complex with laparoscopic procedures. Finally, while not reported in the literature, there is a risk of the stone disappearing in the abdomen during laparoscopy with possible related complications. Previous reports have recommended the incision to reach the periureteral adipose tissue in endopyelotomy, and the stones are fragmented as well in RIRS to achieve stone clearance.[17,18] Based on this background, in the present study a sequential, rather than a simultaneous, rLEP and RIRS procedure was performed. The aim was to decrease the probability of extravasation and minimize the potential effects of UAS and/or flexible ureteroscope on the UPJ. Importantly, sequential treatment may reduce the risk of morbidity, which may be higher when the surgeries are performed simultaneously. Furthermore, sequential treatment can ensure that the flexible ureteroscope has a greater motion capacity following obstruction treatment. In addition, it must be ensured that the ureteroscope has improved control and greater likeliness to reach the stone following the dilatation effect of the inserted stent on the ureter and the elimination of the obstruction. Berkman et al. reported a 90.0% success rate in 41 patients with concomitant UPJO and non-obstructive stones, by using antegrade endopyelotomy and simultaneous stone removal. The authors compared patients with UPJO and stones to patients without stones that underwent endopyelotomy. They reported that the concern that stone fragments could remain in the periurethral adipose tissue following endopyelotomy was unfounded.[14] By performing RIRS after a minimum of 6 weeks from endopyelotomy, we believe that we minimized the potential risks posed by a combined endopyelotomy and lithotripsy procedure. Moreover, it is clear that the retrograde approach does not possess the risks associated with percutaneous access.

In line with previous reports, a lower success rate for RIRS can be observed in cases of greater stone size, higher number of stones, and stones localized in the lower pole and multiple calyxes (**Table 2**). It has been shown that these factors affect stone-free states not only for RIRS but for all treatment modalities.[19] Additionally, Resorlu et al. reported that treatment success also decreased in the presence of anatomical anomalies.[20] However, our study indicates that stone treatment is unaffected by UPJO in sequential rLEP and RIRS treatment.

The presence of crossing veins, severe hydronephrosis, long obstructions and obstructions due to secondary reasons stand for an unfavorable prognosis for endopyelotomy. Treatments to be performed following a first surgery constitute a serious problem for other minimally-invasive procedures.[21] The majority of these factors were considered exclusion criteria in this study. However, we observed that specifically obstruction length and secondary etiology decreased treatment success, in line with the literature. Treatment planning, by combining patients criteria and stone characteristics can help recommend RIRS after retrograde LEP.

RIRS has been reported to be very effective and safe even for patients with high ASA scores.[22] Advances in anesthesia techniques and RIRS's high safety suggest that undergoing anesthesia for a 2nd time for RIRS after rLEP does not pose a risk. As shown by our results, none of our patients manifested complications due to anesthesia. Additionally, patients enrolled in our study, despite undergoing two surgeries, generally had a shorter operative and hospitalization time vs. other techniques. Specifically, grade 3 and more severe complications reported in other studies were not encountered here.

While PNL is typically recommended for stones > 2cm,[23] stones in concomitant UPJO and stone disease that are generally < 2cm (**Table 3**). A link between PNL and a higher rate of complications vs. RIRS has been shown. As a consequence, RIRS is being recommended as one of the primary options for stones < 2cm,[24] suggesting that RIRS will be increasingly popular for the treatment of stone disease following UPJO treatment. Moreover, RIRS has the advantages of its success not being significantly influenced by obesity and lower pole localizations vs. shock wave lithotripsy and PNL, it is easily applied, and it provides high stone-free rates even with limited operator experience.[25]

The present study has some limitations. First, its retrospective character and second, the low number of patients. A greater numbers of cases are needed to validate our study. However, as can be understood from the literature, the present report focuses on an uncommon situation. As a consequence, it is difficult to conduct prospective randomized controlled studies. Since our clinic is a tertiary center for 30-million citizens, the number of patients in this study is not actually very low and is consistent with the literature.

CONCLUSIONS

In patients with UPJ obstruction and renal stones, RIRS performed subsequently to rLEP can be an alternative treatment method. RIRS following rLEP may be preferred in patients with relative contraindications to other minimally-invasive methods (e.g., laparoscopy). We believe that due to its numerous advantages (i.e., short operation time, low morbidity, ease of technique, protection of the surgical area from scarring and capacity to minimize disadvantages such as successive treatment and extravasation of stone), it can be safely used especially in patients with a small single stone and short obstruction.

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