Running Head: Unilateral primary vesicoureteral reflux in pediatric patients

Modified Lich-Gregoir Ureteral Reimplantation for the Treatment of Unilateral Primary Vesicoureteral Reflux in Pediatric Patients: A Comparative Analysis with Medium-Term outcomes

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ABSTRACT

Purpose: To present the medium-term results for the modified Lich-Gregoir (LG) reimplantation technique in the treatment of unilateral primary vesicoureteral reflux (VUR) by comparing patients under and over 12 months of age.

Material and Methods: Data for patients who underwent modified LG surgery between January 2006 and December 2018 were retrospectively reviewed from the hospital data-recording system and patients under the age of 18 years were included in the study. After exclusion criteria, 55 patients in total were included in advanced analysis. The patients were grouped as ≤12 months and >12 months. Demographic characteristics, operative, and postoperative follow-up data were comparatively analyzed.

Results: The mean age was 10.4 ± 2.8 (6-12) and 41.4 ± 18.5 (13-96) months in the ≤12 months and >12 months groups, respectively. Mean operation time and hospitalization time were not significant between the groups. Mean follow-up times were 39.5 ± 14.1 and 38.4 ± 13.2 months, in the ≤12 months and >12 months groups, respectively. There was no significance in terms of complications between the groups and all of the complications in both groups were in grade 1 category according to the Modified Clavien complication classification. One (6.6%) patient in the ≤12 months group and 3 (7.5%) patients in the >12 months group had late (>30 days) febrile UTI, but none of them had a recurrence of VUR. Febrile infection did not recur during the follow-up period in these patients. While recurrent VUR was not seen in any patient in the ≤12 months group (success: 100%), it was seen in 2 (5%) patients in the >12 months group (success rate: 95%) (p=0.38).

Conclusions: The open LG ureteral reimplantation technique is an effective procedure for the treatment of unilateral primary VUR in children both under 12 months and over 12 months of age with minor morbidity.

INTRODUCTION

Vesicoureteral reflux (VUR) is an anatomical and/or functional disorder with potentially serious consequences, such as pyelonephritis, renal scarring, hypertension, and end-stage renal disease. The main management goal is preservation of kidney function by preventing renal scar formation and recurrent urinary tract infections (UTIs) (1). Surgical treatment of VUR includes endoscopic injection therapy, open, laparoscopic, and robot-assisted laparoscopic reimplantation. Although endoscopic injection therapy remains stable over time (>10 years), it has lower success rates especially in patients with high-grade reflux (2,3). Laparoscopic and robotic-assisted laparoscopic techniques are more invasive than endoscopic injection therapy

and their advantages over open surgery are still debated. Therefore, at present, laparoscopic and robotic-assisted laparoscopic approaches cannot be recommended as routine procedures (4). In clinical practice, reimplantation surgeries in the pediatric population are usually performed with open techniques.

To date, various intravesical (Cohen, Politano-Leadbetter and Glenn-Anderson, Gil-Vernet) and extravesical (Lich-Gregoir) techniques were described. Although each method has specific advantages and complications, all of them share the same basic principle of lengthening the intramural part of the ureter and present very high and similar success rates for the treatment of unilateral primary VUR (4). Among these procedures, the most popular one is the Cohen cross trigonal re-implantation technique. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed (5). The Lich-Gregoir (LG) technique is superior to the Cohen technique in terms of hospital stay and operative time. Moreover, it avoids the necessity of urethral and ureteral stenting, which may increase the comfort of patients postoperatively (6). Follow-up data associated with this advantageous technique is limited. In this context, we present the medium-term results of the modified LG technique for the treatment of unilateral primary VUR by comparing patients aged under and over 12 months.

MATERIALS AND METHODS

Study design

In order to conduct the present study, 'data usage approval' was obtained from the authorized hospital management (Private Safa Hospital, date: 22.10.2019). Parents or legal guardians of the patients gave written and verbal informed consent for inclusion in the study and to undergo the procedures described. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and its amendments. Data for patients who underwent modified LG surgery between January 2006 and December 2018 were retrospectively reviewed from the hospital data-recording system and patients under the age of 18 years were included in the study.

Of these, patients with urinary anomalies (ureterocele, duplex system or ectopic ureter), patients who underwent bilateral LG operation, patients with neurogenic bladder, or bowel bladder dysfunction, and patients with incomplete medical records were excluded from the study. After exclusion criteria, 55 patients in total were included in advanced analysis. The patients were grouped as ≤12 months (n=15) and >12 months (n=40). Demographic characteristics, operative, and postoperative follow-up data were comparatively analyzed between the groups.

All patients were evaluated with routine voiding diary, urinary ultrasonography (USG) and voiding cystourethrogram (VSUG). Vesicoureteral reflux was classified by radiologic evaluation on VCUG into five grades (*Grade I*- reflux into the ureter; *grade II*- reflux into the renal pelvis, without any dilation of the calyces; *grade III*- reflux to the renal pelvis with mild dilation of the renal pelvis; *grade IV*- reflux to the renal pelvis with greater dilation of the renal pelvis; *grade V*- reflux to the renal pelvis with ureteral and pelvic dilation) as defined by the International Reflux Study in children (7). Complications were classified according to the modified Clavien-Dindo classification (8). Success was defined as the absence of documented febrile UTI and the absence of recurrence of VUR objectivized by VCUG.

Preoperative assessment

The basic indication for children under 12 months was frequent febrile breakthrough UTIs in spite of continuous antibiotic prophylaxis and circumcision. Surgery indications for children over 12 months included progressive reflux, persistent high-grade reflux (grades IV/V), recurrent UTIs despite medical treatment and/or endoscopic injection therapy, deterioration of renal function, new scar development and non-compliance with medical treatment. Informed consent was obtained from each patient's parents prior to the procedure. The patient assessment included medical history, physical examination, complete blood count, coagulation tests, serum biochemical analysis, urinalysis, urine culture, urinary ultrasonography (USG), and VCUG. Patients were screened for voiding dysfunction or neurogenic bladder with medical history and

physical examination. If indicated, patients underwent urodynamic evaluation. Renal scarring was evaluated with a dimercapto-succinic acid (DMSA) scan on initial presentation. Surgical antibiotic prophylaxis was administered with second-generation cephalosporin.

Operation technique

Following general anesthesia, a Gibson incision was made. The lateral subperitoneal space was opened and the iliac vessels were exposed. Bladder mobilization was achieved by ligation and cutting of the lateral umbilical ligament which crosses the ureter. The ureter was liberated from the iliac vessels towards its entry into the bladder. The future course of the ureter along the posterior bladder wall was chosen and labelled at a distance of 3-5 cm, according to the diameter of the ureter (5:1 ratio). The detrusor was incised in the anterolateral direction until the bladder mucosal protrusion was observed uniformly, creating the new submucosal tunnel. After the ureter was placed in the new submucosal tunnel, the seromuscular layer was closed over it using interrupted 4-0/5-0 synthetic absorbable sutures. At the end of the procedure, the bladder was emptied by direct needle puncture. There was neither instrumentation nor catheter insertion into the urethra during the operation. Routine urethral catheters were inserted in patients with mucosal perforation during dissection. All patients were operated by a single surgeon.

Postoperative follow-up

The placement of the bladder catheter was only indicated in those cases who developed globe vesicale. Postoperative routine follow-up protocol included urinary USG and VCUG at 3 months and urinary USG and DMSA in the first year. If persistent or contralateral reflux was discovered, follow-up VCUG was performed after 6 months of surveillance. Repeat VCUG or DMSA was also requested in case of febrile urinary infection. Antibiotic prophylaxis was terminated with the correction of vesicoureteral reflux confirmed by a single normal VCUG.

Statistical analysis

Statistical comparison of the groups used the SPSS 22.0 (IBM, NY, USA) program. Quantitative data are expressed as mean ± standard deviation and categorical data are expressed with frequency (n) and percentages (%). The Kolmogorov-Smirnov test was used to determine whether the variables were distributed normally or not. The Independent t-test was used to compare the means of two independent groups. Mann–Whitney U test was used to compare the continuous variables. The statistical significance threshold was accepted as $p < 0.05$ for all analyses.

RESULTS

Table-1 presents demographic data and patient characteristics. The mean age was 10.4 ± 2.8 (6-12) and 41.4 ± 18.5 (13-96) months in the groups under and over 12 months, respectively. There were significant differences between the groups with regard to weight, prenatal diagnosis, reflux grade, and HN. All patients received antibiotic prophylaxis. However, all patients in the ≤12 months group and 37.5% of >12 months group had recurrent UTIs. There was history of unsuccessful endoscopic injection in 13.3% of the ≤12 months group and 17.5% of the >12 months group.

Table-2 presents operative and postoperative data. Mean operation time and hospitalization time were not significant between the groups. In 26.6% of the ≤12 months group and 22.5% of the >12 months group, mucosal perforation was seen during dissection and the mucosa was closed as a separate layer in a simple continuous appositional pattern. Only these patients had urethral catheterization. Mean catheterization time was 3.0 days for both groups. None of the patients had postoperative globe vesicale. There was no significance in terms of complications between the groups and all of the complications in both groups were in grade 1 category according to the Modified Clavien complication classification. One (6.6%) patient in the ≤12 months group and 3 (7.5%) patients in the >12 months group had late (>30 days) febrile UTI, but none of them had a recurrence of VUR. Febrile infection did not recur during the follow-up

period in these patients. During the follow-up period, while recurrence VUR was not seen in any patient in the ≤12 months group (success: 100%), it was seen in 2 (5%) patients in the >12 months group (success rate: 95%). However, this difference was not significant.

DISCUSSION

Ureteral reimplantation can be performed with open, laparoscopic, and robot-assisted laparoscopic methods in children (9,10). At present, laparoscopic and robotic approaches cannot be recommended as routine procedures and open surgical techniques still remain the gold standard with good long-term results (4,11,12). Open ureteral reimplantation can be performed with intravesical (Cohen transtrigonal, Politano-Leadbetter, Glenn-Anderson Gill-Vernet and Paquin), and extravesical (Lich-Gregoir) methods. Although the Cohen cross-trigonal ureteral reimplantation is a commonly used technique in children due to the long-term reliable results and broad applicability, it has some disadvantages such as catheter requirements, bladder spasm pain, hematuria, clot retention and need for longer hospitalization.

The Lich-Gregoir extravesical ureteral reimplantation technique causes less morbidity and there is no need for long-term urethral catheterization except in cases where the integrity of the bladder mucosa is impaired during dissection (13,14). The technique was described by Lich and Gregoir in 1961 and 1964, respectively (15,16). In the following years, various modifications of the technique were reported (17). The LG technique has a very high success rate like intravesical methods and the learning curve is shorter. In our series, the success rate was 100% for children under 12 months in the mid-term follow-up in accordance with the literature. Despite high success rates, the main concerns with LG are urinary retention and possible onset of postoperative voiding dysfunction, which in some cases requires catheterization for several weeks especially in cases with bilateral reimplantation. Several series reported bladder voiding dysfunction with an incidence ranging from 3 to 20% in different series (18,19). This is thought to be caused by neurovascular bundle (NVB) injury during ureter

and bladder dissection. Neuropraxia can be reduced with greater knowledge of the topography of the main neural elements, located 1.5-2 cm superior/dorsal to the bladder trigone and medial/dorsal to the ureter (20). We did not detect any voiding dysfunction or urinary retention during midterm follow-up. This is probably due to unilateral VUR in our patients and careful and minimal dissection at the level of the ureterovesical junction. In addition to voiding dysfunction and urinary retention, the LG technique has the risk of ureteric obstruction and periosteal formation of a bladder diverticulum and is not suitable for all kinds of reflux; for example, in cases of obstructed megaureter.

The majority of failed antireflux procedures are the result of inadequate patient selection, or incomplete diagnostic work-up prior to surgery and failure of surgical techniques. In case of failure of reflux surgery, firstly, unspecified previous bladder and/or bowel dysfunctions should be considered. In our series, one of our 2 patients with recurrent reflux from the >12 months group had unstable bladder which we subsequently diagnosed. Anticholinergic therapy completely relieved recurrent reflux. In the other patient, the ureter was very large and recurrence reflux spontaneously regressed at 1 year.

Urinary tract infections are more common after failed reflux surgeries. Postoperative febrile UTI may be an indicator of reflux recurrence or ureteral obstruction. We did not detect reflux in VCUG of 4 patients in total with febrile UTI. So, we considered that febrile UTIs in our patients were caused by temporary ureteral obstruction. If there is an increase in HN degree without reflux in the postoperative follow-up, ureteral obstruction should be suspected. In this case, drainage should be planned with DJ stent or nephrostomy. If there is no improvement with drainage, redo-ureteroneocystostomy (UNC) should be done. In our patients, obstruction was temporary and no patient required drainage or redo-UNC. Guney reported that redo-UNC was required in 8.2% of cases after UNC and that age, sex, laterality of VUR, VUR grade, existence

of primary or secondary VUR, relative renal function on renal scintigraphy, UNC technique, subureteric injection procedure, and ureteral tapering were not risk factors for redo-UNC (21).

Our study showed that complication rates were similar in the ≤12 months group when compared with the >12 months group. Although complication rates were relatively high in both groups, all of these were minor complications that did not require intervention. In addition, the highest complication in both groups was urethral catheter-related pain.

Our study has several limitations. The most important limitation is its retrospective nature. Other potential limitations are that it included a single-center and relatively small number of patients. Larger studies with long-term results are needed to clarify the value of the LG technique, and especially durability in patients under 12 months.

CONCLUSIONS

The open LG ureteral reimplantation technique is an effective procedure for the treatment of unilateral primary VUR in children both under 12 months and over 12 months with satisfactory medium-term outcomes. Although complication rates are relatively high, all of the complications are minor complications. The primary cause of failure is previous bladder and bowel dysfunction. Therefore, preoperative bladder and bowel dysfunction should be evaluated carefully.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1: Demographic data and patient characteristics

Parameters	**≤12 Months** (n=15)	**>12 Months** (n=40)	**p**
Age, month (mean ± sd)	10.4 ± 2.8	41.4 ± 18.5	***<0.001***
Sex *n,(%)*			0.84
Male	6 (40%)	18 (45%)	
Female	9 (60%)	22 (55%)	

Weight kg (mean ± sd)	8.9 ± 2.3	21.4 ± 6.5	***<0.001***
Prenatal diagnosis *n, (%)*	11 (73.3%)	10 (25%)	***<0.001***
Reflux side *n, (%)*			0.87
Right	6 (40%)	17 (42.5%)	
left	9 (60%)	23 (57.5%)	
Reflux grade *n, (%)*			***<0.001***
grade 3	2 (13.3%)	30 (75%)	
grade 4	7 (46.6%)	6 (15%)	
grade 5	6 (40%)	4 (10%)	
HN *n, (%)*			***0.029***
grade 0	-	7 (17.5%)	
grade 1-2	2 (13.3%)	10 (25%)	
grade 3	10 (66.6%)	19 (47.5%)	
grade 4	3 (20%)	4 (10%)	
History of endoscopic injection n, (%)	2 (13.3%)	7 (17.5%)	0.72

sd; standard deviation

VUR: vesicoureteral reflux

HN: hydronephrosis

Parameters	**≤12 months** (n=15)	**>12 months** (n=40)	**p**
Operation time, *min (mean ± sd)*	57.4 ± 11.2	60.4 ± 14.5	0.37
Perioperative mucosal perforation, *n, (%)*	4 (26.67%)	9 (22.5%)	0.75
Hospitalization time, *day (mean ± sd)*	2.9 ± 0.4	3.1 ± 0.5	0.22

Postoperative urinary retention, *n, (%)*	0	0	
Urethral catheter time, *day (mean ± sd)*	3	3	
Complications, *n, (%),* *(Modified Clavien classification)*	6 (40%)	17 (42.5%)	0.87
spasm pain due to catheter (grade 1)	3 (20%)	9 (22.5%)	0.36
macroscopic hematuria (grade 1)	2 (13.33%)	3 (7.5%)	0.51
febrile UTI (grade 1)	1 (6.67%)	3 (7.5%)	0.91
wound infection (grade 1)	0	2 (5%)	0.38
Follow-up time, *months (mean ± sd)*	39.5 ± 14.1	38.4 ± 13.2	0.42
Recurrent reflux, *n, (%)*	0	2 (5%)	0.38
Postoperative HN, *n, (%)*			
grade 1	3 (20%)	7 (17.5%)	0.90
grade 2	1 (6.67%)	3 (7.5%)	

Table 2: Operative outcomes and postoperative follow-up data

UTI: urinary tract infection

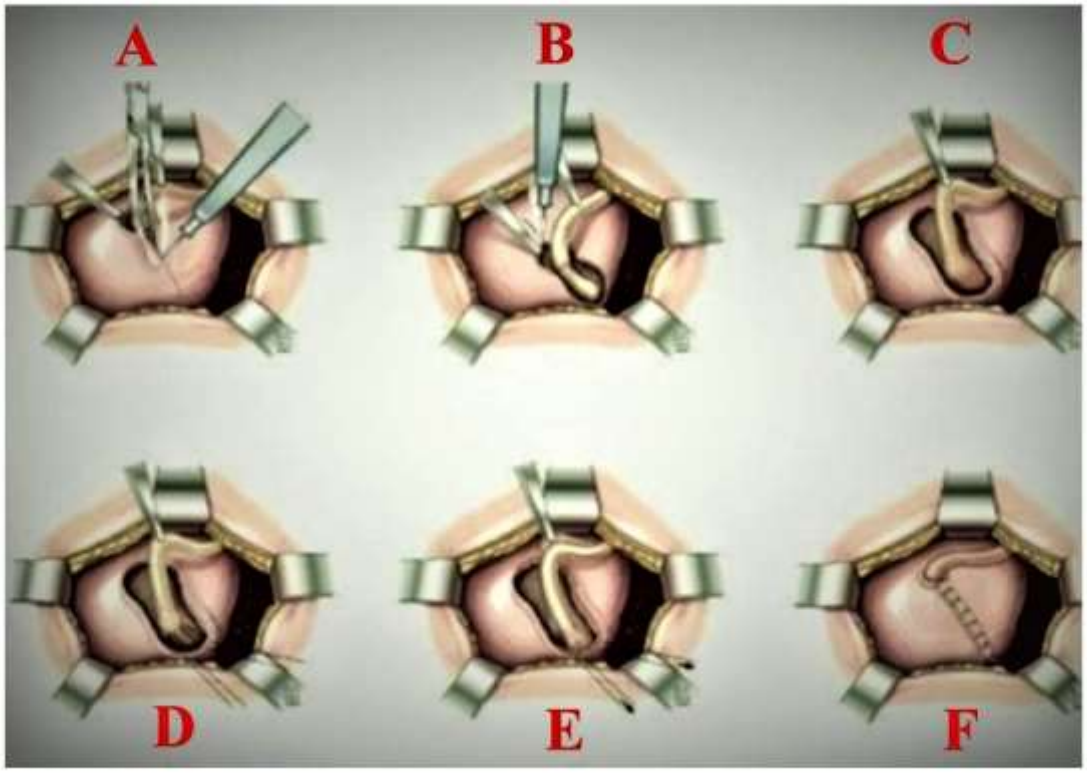

Figure-1: Stages of the modified LG operation. Complete division of the detrusor muscle to the epithelium cutting in an anterolateral direction 3–5 cm from the ureter **(A,B,C,)**. Placing the ureter in the groove in contact with the bladder epithelium **(D,E)** and loose closure of the muscle over the ureter with interrupted 4-0/5-0 synthetic absorbable sutures **(F).**