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A Novel Ureterovesical Anastomosis Techniques in Adult Kidney Transplantation

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1. Abstract

1.1. Introduction

Urological complications following kidney transplantation is strongly negatively correlated with long-term graft survival. The Lich Gregoir ureterovesical anastomosis technique is the most common choice for kidney transplantation, but still associated with certain urological complications. Here, we introduced the split-cuff nipple technique in adult kidney transplantation and compare the outcomes with the Lich–Gregoir technique.

1.2. Methods

We retrospectively collected adult kidney transplant patients underwent ureterovesical anastomosis with the split-cuff nipple or Lich–Gregoir technique at our center between July 2019 and July 2022. The split-cuff nipple technique was described with a detailed technical description. Primary outcome was the incidence of urological complications.

1.3. Results

We reviewed 229 patients in our center: 143 in the split-cuff nipple group and 86 in the Lich–Gregoir group. All recipients had at least 3 months postoperative follow-up. The baseline characteristics were comparable among two groups. Hematuria was more common in the split-cuff nipple group (14.7%) than in the Lich–Gregoir group (5.8%), but the difference was not statistically significant ($p = 0.052$). Ureteral stenosis occurred in 5 patients (3.5%) in the split-cuff nipple group and 4 patients (4.7%) in the Lich–Gregoir group ($p = 0.731$). The two groups had similar ureterovesical anastomosis times, delayed graft function, urinary tract infection and creatinine blood levels at 3 months ($p = 0.595$, 0.441, 1.00 and 0.363, respectively).

1.4. Conclusions: Our research revealed that the split-cuff nipple ureterovesical anastomosis technique is a feasible and safe method in adult kidney transplantation. Compared with the Lich–Gregoir technique, no significant difference with respect to urological complications was observed.

2. Introduction

Kidney transplantation is currently the most established organ transplant surgery and the most effective treatment for end-stage renal disease. Vascular and ureterovesical anastomoses are two key steps during the surgery of kidney transplantation. Urological complications following kidney transplantation are associated with ureterovesical anastomosis, with the prevalence of urological complications reaching up to 6.2% in a recent study [1]. The urological incidence of complications varies with different ureterovesical anastomosis methods [2]. Most urological complications, including urine leakage, ureteral stenosis, hematuria, and vesicoureteral reflux occur in the first 3 months after kidney transplantation [3,4]. These complications result in excess morbidity and substantial cost to patients [5]. Most importantly, urological complications following kidney transplantation is strongly negatively correlated with long-term graft survival [6]. Among the most severe complication is ureteral stenosis, it always requires open surgery or endoscopic techniques, which brings much trauma for patients [7]. Lich–Gregoir (LG) extravesical ureterovesical anastomosis is recommended by the current European Association of Urology (EAU) guidelines [8]. The LG technique involves direct anastomosis of the distal ureter to the bladder mucosa, and then part of the ureter is embedded below the muscular layer of the bladder [2]. Although LG ureterovesical anastomosis is the most

commonly used technique, there continues to be a certain rate of urological complications [9,10]. Our center has applied the split-cuff nipple (SN) extravesical ureterovesical anastomosis in radical cystectomy with orthotopic ileal neobladder since 2002 and found that it has advantages due to anti-reflux properties and low complications [11]. We applied the SN technique in adult kidney transplantation ever since 2019. The SN technique consists of a nipple formed by the eversion of the distal ureter, then the distal ureter mucosa is anastomosed to all layers of the bladder after the ureter nipple is placed into the bladder lumen [12]. However, SN ureterovesical anastomosis has not yet been reported in adult kidney transplantation and has not been compared to the LG technique. The purpose of this study was to introduce the novel ureterovesical anastomosis technique in adult kidney transplantation and evaluate the safety and feasibility, also compare urological complications and outcomes with LG technique.

3. Materials and Methods

3.1. Study Design

This is a retrospective single-center cohort study that was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, whose ethical number was SYSKY-2023-538-01. We collected data on adult kidney transplant patients who underwent ureterovesical anastomosis with the Lich–Gregoir or split-cuff nipple technique between July 2019 and July 2022 at Sun Yat-sen Memorial Hospital. All patients had more than 3 months of postoperative follow-up. The exclusion criteria were multiple organ transplant, donor kidney combined with pyelolithotomy simultaneously, ureteral injury or ureteral dysplasia. Due to the retrospective nature of the study, Informed consent was not obtained from the individual participants. The primary outcome was urological complications after transplantation, which were graded in accordance with the modified Clavien–Dindo classification system [13]. The secondary outcomes included ureterovesical anastomosis time, delayed graft function, urinary tract infection (UTI) and creatinine blood levels at 3 months. Urological complications, including urine leakage, ureteral stenosis, hematuria, hydronephrosis after stent removal and pyelonephritis, were assessed on a nominal scale (presence or absence). Urine leakage was defined as urine leaking from the ureterovesical anastomosis. Ureteral stenosis was determined by increased creatinine and imaging evidence of ureteric stricture. Hematuria was defined as immediate macroscopic hematuria requiring catheter irrigation and/or operation. Patients who had dialysis during the first week after transplantation were defined as having delayed graft function.

3.2. Surgical Techniques

Ureteral preparation and bladder exposure are conducted in two techniques using the same method. In the LG technique, the distal ureter is sutured to the bladder mucosa, and then part of the ureter is embedded below the muscular layer of the bladder to form a tunnel to prevent reflux [2]. In the SN technique, the distal ureter is initially spatulated for approximately 0.5 cm along the long axis (Figure 1 A, Figure 2 A). A double-J stent (4.7-Fr Bard 14 cm) is placed into the ureter under direct vision. The split-cuff nipple is created by everting the spatulate ureter upward and then 4-0 absorbable sutures are used to stitch the edge of ureter to the ureteral adventitia (Figure 1 B, Figure 1 C). Notably, the nipple is a half nipple not a whole circumferentially wrapped nipple (Figure 2 B). Next, the bladder is filled with 200 ml saline via a Foley catheter, a 1 cm incision is then made in the anterior wall of the bladder. Then, we suture the full-thickness of bladder to the ureteral adventitia using simple interrupted suture technique but without knotting (Figure 2 C). Finally, when the sutures are knotted and anchored (Figure 1 D), the split-cuff nipple is inserted into the bladder simultaneously (Figure 2 D). A double-J stent is placed routinely in the two techniques.

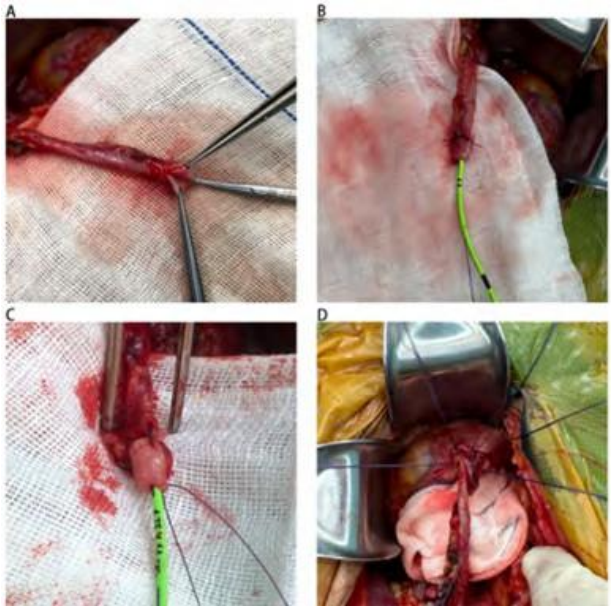

Figure 1: (A) the distal ureter is spatulated for 0.5 cm, (B) a 4.7-Fr stent is inserted, the ureter is everted to form a nipple, two corners are sewn apart to ureteral adventitia, (C) the edges of ureter are interrupted suture to the upward of ureter, (D) suture the full-thickness of bladder to the ureteral adventitia using simple interrupted suture.

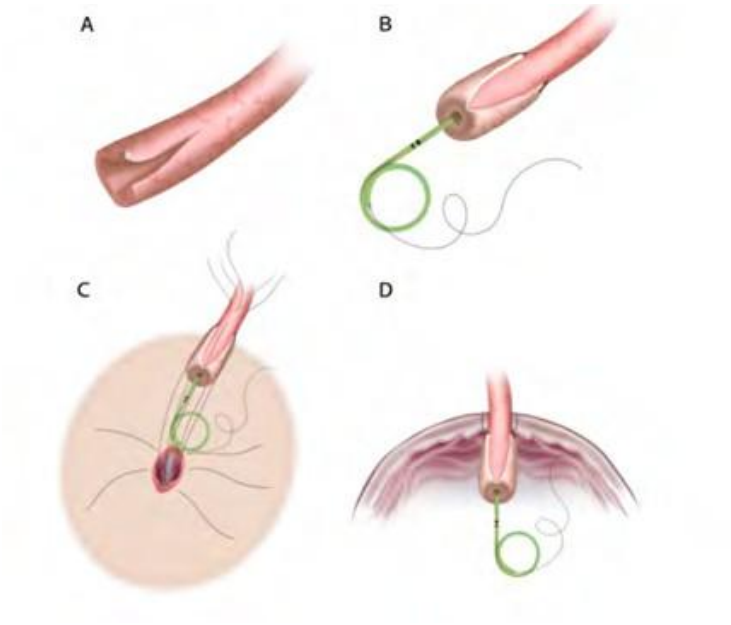

Figure 2: (A) the distal ureter is spatulated for 0.5 cm, (B) the nipple is a half nipple not a whole circumferentially wrapped nipple (C) the ureteral adventitia is anastomosed to full-thickness of the bladder with 5 or 6 interrupted sutures but without knotting, (D) knot and anchor these sutures, insert the split-cuff nipple into the bladder simultaneously.

3.3. Perioperative Management

The immunosuppressive therapy regimen was comprised of induction agents such as anti-thymocyte immunoglobulin or basiliximab, and the maintenance agents included prednisone, tacrolimus, mycophenolate sodium or mycophenolate mofetil. The current literature and EAU guidelines recommend a prophylactic ureteral stent to minimize urinary tract complications in kidney transplant recipients [3,8,14]. Thus, a double-J stent was placed routinely in the two techniques performed in our center. A routine contrast enhancement ultrasound was performed on all patients on postoperative day 3 or 4. The Foley catheter was removed in the second postoperative week. After removing the Foley catheter, we removed the double-J stent through a cystoscope as soon as possible (Figure 3).

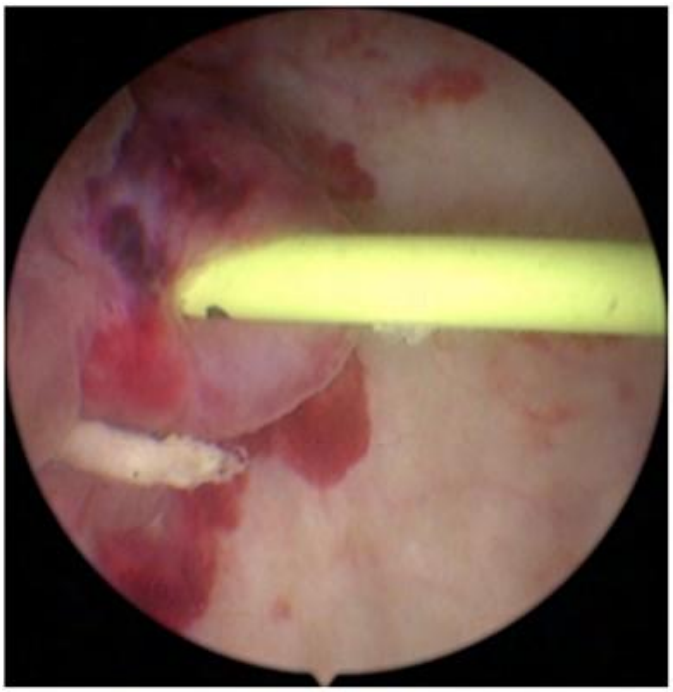

Figure 3: The split-cuff nipple and stent in the bladder under cystoscopy.

3.4. Follow-Up Methods

All patients had at least 3 months of postoperative follow-up, which was performed by outpatient reviews. Postoperative follow-up was conducted every week during the first 3 months, every 2 weeks during the second 3 months, and every month thereafter. The follow-up visits consisted of medical history, physical examination and routine blood tests. A routine ultrasound was performed two weeks after the double-J stent was removed.

3.5. Statistical Analysis

Epidata 3.1 software was used for data processing, and IBM SPSS Statistics software version 25.0 was used for statistical analysis. Continuous parametric variables were described as medians (quartile 1, quartile 3) and were compared between the groups using the Mann–Whitney test or T test. Normality and homogeneity of variance were also checked. Categorical variables were described as frequencies (percentages) and were compared using Fisher's exact test. Two-tailed p values less than 0.05 were considered statistically significant.

4. Results

From July 2019 to July 2022, a total of 229 kidney transplant patients were enrolled. The SN technique was applied in 143 patients (62.4%), and the LG technique was applied in 86 patients (37.6%). The baseline characteristics of the study cohort are shown in Table 1. On the donor side, the cohort is generally donation after brain death. Serum creatinine was within the normal range for most donors, and very few donors had diabetes mellitus. There were no statistically significant differences between the SN and LG groups in age, sex, diabetes mellitus or preoperative creatinine. On the recipient side, the majority of our recipients were hemodialysis patients in the SN and LG group (74.1% vs. 67.4%). The preoperative creatinine was

comparably high in both groups, which was related to ineffective dialysis. The median pretransplant duration on dialysis in the SN and LG groups was 14.5 (7.6, 36.2) months and 12.5 (6.1, 30.2) months, respectively (p = 0.233). The basic characteristics of the recipients were not significantly different between the groups. Double-J stents were placed routinely in the two groups and were removed at a median of 13 [11,17] days and 14 (13, 16) days posttransplantation (p = 0.291).

There were no statistically significant differences in the outcomes of the recipients within the two cohorts in Table 2. No urine leakage occurred in either group. In the SN group, 21 patients (14.7%; 95% confidence interval [CI], 921%) developed hematuria (Grade I), which was improved by catheter irrigation. One patient (0.7%; 95% CI, 0-2%) developed pyelonephritis (Grade I). Two patients (1.4%; 95% CI, 0-3%) had hydronephrosis after stent removal (Grade I) but had normal creatinine levels. Eight patients (5.6%; 95% CI, 1-7%) developed hematuria requiring transfusions (Grade II), and 5 patients (3.5%; 95% CI, 0-7%) developed ureteral stenosis (Grade III). Three patients with ureteral stenosis were cured by retrograde endoscopic balloon dilation and double-J stent placement for 6 months, and 2 patients went through ureteroneocystostomy. In the LG group, no hydronephrosis occurred after stent removal, and 5 patients (5.8%; 95% CI, 1-11%) developed hematuria (Grade I), which was improved by catheter irrigation. One patient (1.2%; 95% CI, 0-3%) developed pyelonephritis (Grade I), 1 patient (1.2%; 95% CI, 0-3%) developed hematuria requiring transfusion (Grade II), and 4 patients (4.7%; 95% CI, 0-9%) developed ureteral stenosis (Grade III). Three patients with ureteral stenosis were failed by endoscopic balloon dilation and double-J stent placement for 6 months, and 1 patient went through ureteroneocystostomy. No differences were demonstrated in UIT and delayed graft function in the groups. The ureterovesical anastomosis times with the SN and LG techniques were 27 (95% CI, 24.74-27.82) and 25 (95% CI, 23.69-28.45) minutes, respectively (p = 0.595). The patients' renal functions recovered well and were similar between the two groups at 3 months posttransplant.

Table 1: Demographic and clinical characteristics of patients in the two groups.

Variables	SN (N = 143; 62.4%)	LG (N = 86; 37.6%)	p Value*
Donor			
Age	42 (29, 48)	37 (29.5, 48)	0.155
Female, n (%)	29 (20.3)	20 (23.3)	0.620
BMI (kg/m^2)	22.49 (20.31, 23.88)	22.49 (20.76, 25.95)	0.084
Donation after brain death, n (%)	141 (98.6)	84 (97.7)	0.632
Diabetes mellitus, n (%)	4 (2.8)	0	0.300
Preoperative creatinine (mg/dl; *N* = 227)	0.83 (0.61, 1.10)	0.80 (0.64, 1.10)	0.684
Recipient			
Age	45 (37, 54)	45 (32.75, 55)	0.971
Female, n (%)	47 (32.9)	29 (33.7)	1.000
BMI (kg/m^2)	22.86 (20.29, 24.96)	21.89 (19.69, 24.56)	0.294
Panel reactive antibodies >0, n (%)	48 (33.6)	24 (27.9)	0.383
Preoperative creatinine (mg/dl)	9.33 (7.49, 11.41)	9.97 (8.02, 12.72)	0.141
Preoperative BUN (mg/dl)	51.26 (40.33, 66.38)	52.94 (40.54, 79.1)	0.568
Diabetes mellitus, n (%)	23 (16.1)	17 (19.8)	0.478
Hemodialysis, n (%)	106 (74.1)	58 (67.4)	0.292
Duration on Dialysis (mo)	14.5 (7.6, 36.2)	12.5 (6.1, 30.2)	0.233
Retransplantation, n (%)	3 (2.1)	2 (2.3)	1.000
HLA mismatch ≥3, n (%)	126 (88.1)	67 (77.9)	0.060
Warm ischemia time (min)	7.0 (6.0, 8.0)	7.0 (5.0, 9.0)	0.966
Ureteral stent removal (d; *N* = 228)	13 (11, 17)	14 (13, 16)	0.291

SN = Split-cuff nipple; LG = Lich–Gregoir; BMI = body mass index; HLA = human leukocyte antigen.
Estimates were given as medians (quartile 1, quartile 3) or frequencies (percentages).
* *p* Values were calculated using Wilcoxon rank-sum or T test for continuous and Fisher's exact test for categorical variables

Table 2: Urological complication and outcomes in two groups.

Variables	SN (N = 143; 62.4%) No. or Median	95% CI	LG (N = 86; 37.6%) No. or Median	95% CI	P Value
Urological complications †, (%)					
Grade I					
Hematuria	21 (14.7)	(0.09, 0.21)	5 (5.8)	(0.01, 0.11)	0.052
Pyelonephritis	1 (0.7)	(0.00, 0.02)	1 (1.2)	(0.00, 0.03)	1.000
Hydronephrosis after stent removal	2 (1.4)	(0.00, 0.03)	0	(0.00, 0.00)	0.529
Grade II					
Hematuria (requiring transfusion)	8 (5.6)	(0.01, 0.07)	1 (1.2)	(0.00, 0.03)	0.159
Grade III					
Stenosis	5 (3.5)	(0.00, 0.07)	4 (4.7)	(0.00, 0.09)	0.731
UTI, (%)	25 (17.5)	(0.11, 0.24)	15 (17.4)	(0.09, 0.26)	1.000
Creatinine at 3 months (mg/dl; *N* = 218)	1.40 (1.16, 1.71)	(1.44, 1.71)	1.35 (1.15, 1.61)	(1.33, 1.53)	0.363
Delayed graft function, (%)	9 (6.3)	(0.02, 0.10)	8 (9.3)	(0.03, 0.16)	0.441
Ureterovesical anastomosis time (mins)	27 (17, 35)	(24.74, 27.82)	25 (15, 33)	(23.69, 28.45)	0.595

SN = Split-cuff Nipple; LG = Lich–Gregoir; CI = confidence interval; UTI = urinary tract infection.
Estimates were given as median (quartile 1, quartile 3) or frequency (percentage).
† Grades were based on modified Clavien–Dindo classification system.

5. Discussion

By retrospective analysis of 229 kidney transplant patients at our center between July 2019 and July 2022, the present study showed no differences between the SN technique and the LG technique in terms of urological complications, delayed graft function, ureterovesical anastomosis time or UTI. However, when ureteral stenosis occurred, the success rate of the retrograde endoscopic procedure seems to be higher in the SN technique, because it's easier to find the ureteral orifice. Urological complications after kidney transplantation are related to significant patient morbidity, especially graft loss and mortality [15]. Ureterovesical anastomosis is associated with the urological complication rate. Ureterovesical anastomosis is divided into intravesical and extravesical methods. The Politano-Leadbetter technique is the most commonly used intravesical method, and the extravesical methods mainly include the Lich–Gregoir and Taguchi techniques. Currently, the EAU guidelines recommend the Lich–Gregoir technique as the first choice in kidney transplantation (8), with a lower urological complication rate than other techniques [16]. Turner-Warwick et al. in 1967 first introduced the split-cuff nipple technique in cystoplasty [17]. In 2010, our center reported the split-cuff nipple technique applied in orthotopic ileal neobladder after radical cystectomy with a reliable anti-reflux effect [11]. Reported the nipple-valve ureteroneocystostomy technique in pediatric kidney transplants with a low rate of pyelonephritis after surgery [18]. The split-cuff nipple technique involves spatulating the distal ureter and everting it to form a half nipple, then inserting it into the bladder to form a permanent intraluminal nipple. Theoretically, as the bladder fills, compression around the nipple causes closure of the ureteral lumen, reducing the chance of vesicoureteral reflux. In addition, the blood supply could be preserved better due to the interrupted suturing, which may reduce the incidence of anastomotic stenosis. However, our study showed no statistically significant difference in various urological complications between the SN and LG techniques. Although, the most common early postoperative urological complication after transplantation reported in the researches was urine leakage [10,16]; no urine leakage occurred in either of the two groups in our study. Hematuria was the most common complication in both groups, and the incidence of hematuria in the SN group was higher than that in the LG group. There seemed to be more patients with hematuria in the SN group (21 vs 5). However, there is no statistically significant difference (p = 0.052). All the patients with hematuria improved after bladder irrigation. All the patients' hematuria was graded as low by the Clavien–Dindo classification (1 or 2), and no endoscopic or surgical treatment was needed. The higher incidence of hematuria in the SN group may be due to the fewer sutures in that group than in the LG group, and simple interrupted sutures were used to anastomose the ureter mucosa to the full-thickness bladder (Figure 1 C). Another possible explanation is that by inserting the nipple into the bladder, the ureteral stump was exposed to urine and the hemostatic fibrin clot would be dissolved by urokinase [19,20]. Although the hematuria in the SN group was mild and manageable, we still do not recommend the use

of the split-cuff nipple technique for ureterovesical anastomosis in kidney transplant patients with preoperative anticoagulation or who need early postoperative anticoagulation, because we found patient who taking anticoagulants before surgery had severe hematuria which requiring transfusions after surgery. Ureteral stenosis is the most common urological complication after transplantation. Reported a national cohort study among 3023 kidney transplant patients with an incidence of ureteral stenosis at one year of 5.8% (1). At present, a total of 9 kidney transplant patients (3.9%) developed ureteral stenosis in our center, including 5 in the SN group (3.5%) and 4 in the LG group (4.7%). Among the SN group, 3 patients were improved by retrograde endoscopic balloon dilation and double-J stent placement for 6 months, and there was no recurrence in the long-term follow-up. However, in the LG group, only 1 patient was successfully treated by one-stage retrograde endoscopic treatment and the other 2 patients were converted to PCN. These 3 patients recured immediately after double-J stent placement for 6 months. Currently, endoscopy is the first choice for the treatment of ureteral stenosis after kidney transplantation [21], and a minimally invasive retrograde approach should be preferred [22]. PCN and reoperation following kidney transplantation have a significant impact on kidney transplant patients, with increased morbidity and mortality [23,24]. Because of the free nipple in the bladder (Figure 3), it is easy to find the ureteral orifice under endoscopy to manage postoperative stenosis, stones and other complications with a retrograde approach. In addition, most of the ureteral stenosis in the SN group could be treated by retrograde balloon dilation and double J stent insertion. While in the LG group, it was difficult to find the ureteral orifice in the bladder, which made retrograde management difficult (1/4). Of note, none of the patient with ureteral stenosis in the LG group succeed with the balloon dilation. As far as we could see, the SN technique may make it easier to manage the complications after kidney transplantation such as ureteral stenosis by the retrograde approach. The ureteral stenosis in the SN group seems to be easier to manage through the simple balloon dilation. Yet now, there was no statistic difference, found and more cases are needed. In this study, we describe the SN ureterovesical anastomosis technique in detail. At first, the technique was used in the bowel segments for lower urinary tract reconstruction to prevent reflux, and the nipple was always totally circumferentially wrapped, which has the risk of obstructing the ureter or necrosing the nipple [25]. We sutured the two corners of the distal ureter to the ureteral adventitia separately to form a half circumferentially wrapped nipple, reducing the risk of ureteral obstruction and nipple necrosis. Some researchers have reported that the long nipple in the bladder carries the risk of ischemic necrosis and stenosis [17]. Our experience found that the most appropriate length is no more than 0.5 cm, and further studies are needed to confirm this finding. In summary, the study evaluated the incidence of urological complications and outcomes with the SN technique. Although our study was a retrospective study with reduced strength, to the best of our knowledge, this is the first study comparing the SN and LG ureterovesical anastomosis techniques in kidney transplantation.

6. Conclusion

The incidence of urological complications and perioperative outcomes in the split-cuff nipple technique was similar to that in the Lich–Gregoir technique in kidney transplantation. We consider that the split-cuff nipple ureterovesical anastomosis technique is a feasible and safe method in adult kidney transplantation.

7. Acknowledgement

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