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Original Article

Comparison of anti-reflux mechanism between Double-J-Stent and standart Double-J-Stent use for risk of BK nephropathy and urinary tract Infection in kidney transplantation

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Abstract: Objectives: There are studies that show that double J stenting (DJS) increase BK nephropathy (BKN) 4 fold. DJS may cause vesicoureteral reflux (VUR) with normal bladder contraction. The aim of this study is to comparison risk of BKN, urinary tract infections (UTI) and postoperative urologic complications with the use DJS with anti-reflux device (ARD-DJS) and standart double J stent (St-DJS). Matherial and methods: Ninety patients (male/female: 50/40) that had undergone kidney transplantations in Diyarbakır Training and Research Hospital and Dicle University, Faculty of Medicine Hospital between January 2012 and April 2015 were enrolled in the study. Demographic data, immunosuppression protocols, presence of rejection, graft loss, postoperative urologic complications, UTI, plasma BK levels of the patients were evaluated retrospectively. Results: Median and IQR follow up time for ARD-DJS and St-DJS patients were 14 (12-18) months and 25 (16-30) months respectively. Five cases (5.5%) had BK viremia (P=0.025). All 5 cases with BK viremia were St-DJS users. Conclusion: As a result for postoperative UTI and postoperative urinary complication risk there were no statistically significant difference between ARD-DJS use and St-DJS use during ureteral anastomosis. BKN univariate analysis were significantly less than those st-DJS used. Risc factors were evaluated. But results were not statistically significant in the logistic regression analysis. We think that to demonstrate this benefit, we need randomized controlled studies with more patients and longer follow up.

Keywords: Double J stenting, anti-reflux device, BK nephropathy

Introduction

BK virus (BKV) was first isolated in a kidney transplanted patient who had ureteral stenosis in 1971 [1]. BKV is found in uroepithelial cells and they are asymptomatic and latent in healthy people who do not use immunosuppressive drugs [2]. After kidney transplantation with the commencement of immunosuppressive therapy, BKV reactivation, viruria, viremia and than nephropathy may develop [3]. About 10-20% of the kidney transplanted patients develop BKV viremia and 5-10% of them BKV nephropathy (BKN) [4]. Graft loss is seen in 10-80% of the BKN cases [5]. Risk factors for BKV infections are agressive immunosuppression, high human leukocyte antigen (HLA) mismatch, ureteral stent use, rejection and prolonged ischemia time [6-11]. Despite intensive immunosuppression, native kidney BKN is rarely observed in non kidney transplantations [10, 11]. There is a debate about role of double J stenting (DJS) for BKN. There are studies that show that DJS increase BKN 4 fold [4, 12]. This fact was explored with experimental animal models. Erosion, superficial epithelial destruction, ulceration on transitional epithelium and inflammatory changes were shown on animal ureters

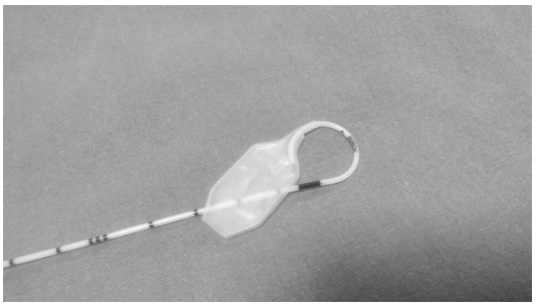

Figure 1. Anti-reflux mechanism double J stenting (ARD-DJS).

with DJS [13, 14]. Studies have shown that situations that cause persistant hydronephrosis such as kinking of posttransplant ureter and ureteral stenosis might involve a dynamic role in the pathogenesis of polyoma virus associated nephropathy by enabling ureteral reflux [15]. DJS may cause vesicoureteral reflux (VUR) with normal bladder contraction [16]. As far as we know that there is not a study that investigate anti-reflux device double J stent (ARD-DJS) use and BKN risk (**Figure 1**). The aim of this study is to comparison risk of BKN, UTI and postoperative urologic complications with the use DJS with anti-reflux device and double J stent (ARD-DJS).

Materials and methods

Ninety patients (male/female: 50/40) that had undergone kidney transplantations in Diyarbakır Training and Research Hospital and Dicle University, Faculty of Medicine Hospital between January 2012 and April 2015 were enrolled in the study. The study was conducted in accordance with the principles of the 2008 Helsinki Declaration. Informed consent was obtained from all the patients. Seventy six of the patients had living donor and 14 of them had deceased donor kidney transplantation. Demographic data, immunosuppression protocols, presence of rejection, graft loss, postoperative urologic complications, urinary tract infections (UTI), plasma BK levels of the patients were evaluated retrospectively (**Table 1**).

Immunosuppression and prophylaxis

Basiliximab (20 mg at days 0 and 4 of operation) or anti-thymocyte globulin (ATG; for high risk patients, 3 mg/kg during operation and 1.5 mg/kg at postoperative days 1 and 2) were used as induction treatment. Methylprednisolone 1000 mg was given intraoperatively. Methylprednisolone dose was decreased by half everyday and 20 mg oral prednisolone was started on the 6th postoperative day for daily use. Oral prednisolone dosage was reduced gradually to reach 5 mg a day at the first year after transplantation. Calcineurin inhibitors (tacrolimus or cyclosporin) and mycophenolate mofetil (MMF; 2 g a day in two divided doses) or mycophenolate sodium (MMF; 1440 mg a day, in two divided doses) were used as maintenance immunosuppression. MMF was used as 600 mg/m^2 in two divided doses in children. We considered both mycophenolate mofetil and mycophenolate sodium in doses described above as the same drugs in our study. Everolimus was used in only one case (plasma level of the drug was targeted as 8-10 mg/dl). Trimethoprim/sulfamethoxazole and valganciclovir (450 mg a day) was prescribed for Pneumocytis jirovecii and cytomegalovirus (CMV) prophylaxis for 6 months after the transplantation. Acute rejection was diagnosed by kidney biopsy. Acute cellular rejection was treated with intravenous pulse methylprednisolone or ATG depending on the severity of the rejection. Plasmapheresis was added for acute humoral rejection. Delayed graft function (DGF) was described as a need for hemodialysis in the first week of kidney transplantation.

Surgical technique

Open nephrectomy technique was applied for living donors. Extravesical technique (Lich-Gregoir) was applied to all transplanted patients for ureteroneocystostomy (UNS). Types of DJS used were dependent on the choice of the centers and surgeons. Cases were grouped later by whether their DJS had anti-reflux mechanism or not (St-DJS vs ARD-DJS). Surgical drains were placed to all patients to the operation side. Urinary catheters were removed on the 5th postoperative day. Surgical drains were removed if there were no urinary leak and after urinary catheters were removed. All DJSs were removed by cystoscopy under local anesthesia at 4th postoperative week. Urinary complication was described as presence of urinary leak and stenosis at UNS.

Follow up

All patients were followed up closely for renal functions, UTI, BK viremia and BKN after kidney transplantation. Fever, elevated creatine

Table 1. Comparison of the cases with ARD-DJS and non ARD-DJS use during kidney transplantation

	St-DJS n=44	ARD-DJS n=46	*P* value
Sex F/M	22/22	18/28	0.315
Age (years)	32.2 ± 16 (7-65)	32.8 ± 12.6 (17-60)	0.286
Median and IQR follow up time after kidney transplantation (months)	25 [16-30]	14 [12-18]	<0.001
Living donor/deceased donor	33/11	43/3	0.016
Preemptive	14 (31.8%)	20 (43.4%)	0.25
Induction			<0.001
No	18 (40.9%)	0	
ATG	16 (36.4%)	7 (15.2%)	
Basiliximab	10 (22.7%)	39 (84.8%)	
Treatment of rejection: pulse steroid/ATG and pulse steroid	1/4	2/1	0.46
Number of rejections	5 (11.3%)	3 (6.5%)	0.48
ATG use	17 (38.6%)	8 (17.4%)	0.024
UTI	18 (40.9%)	12 (26.1%)	0.14
UTI>3	5 (11.3%)	2 (4.3%)	0.26
Graft loss	2 (4.5%)	0	0.24
DGF	6 (13.6%)	1 (2.1%)	0.056
BKV	5 (10.8%)	0	0.025
Last Cr level (mg/dl) med and IQR	1 [0.76-1.27]	1 [0.86-1.34]	0.59

ARD-DJS: anti-reflux mechanism double J stenting; st-DJS: standart-DJS; ATG: anti thmocyte globulin; UTI: urinary tract infection; DGF: delayed graft function; BKV: BK viremia; Cr: creatine.

(Cr), high C-reactive protein (CRP), bacteria >100,000 colonies/ml in urinary culture were associated with UTI. First BKV tests were done on 1st postoperative month. All transplanted patients were tested for BKV from their serum by polymerase chain reaction (PCR) monthly in the first year after transplantation. All the patients were followed up at the posttransplant period for at least 12 months. Cases with >500 copies/ml by two or more consecutive measurements were accepted as having viremia. Immunosuppression dose was reduced was reduced when there was higher viremia load (>5,000 copies/ml). Firstly MMF was discontinued and prednisolone dose was reduced. If viremia continued, calcineurin dose was reduced. Leflunomide was used for patients with BK nephropathy. Kidney biopsy was performed to all cases with viremia for excluding BKN.

Statistical analysis

Statistical analyses were performed using the SPSS software version 16. The variables were investigated using (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using medians and interquartile range (IQR) for the non-normally distributed and ordinal variables. The proportions of patients with UTI, recurrent UTI, ATG use, preemptive transplantation and BKN were grouped by types of DJS using cross tabulations. The Chi-square test or Fisher's exact test, where appropriate, were used to compare these proportions in diferent groups. Blood Cr measurements were not normally distributed; nonparametric tests were conducted to compare these parameters. The Mann-Whitney U test was used to compare relationship between blood Cr levels and use of the ARD-DJS. Logistic regression analysis was used to determine independent predictors of patient outcome. A *P*-value of less than 0.05 was considered to show a statistically significant result.

Results

Results of 90 patients who had kidney transplantation in two centers between January 2012 and April 2015 were evaluated retrospectively. Median and interquartile range (IQR) of age and time from kidney transplantation of the patients were 33 [21-42] years and 25,02 [20-31] months respectively.

Median and IQR follow up time for ARD-DJS and St-DJS patients were 14 [12-18] months and 25 [16-30] months respectively. Preemptive kidney transplantation was performed to 34

(37.8%) of the patients. Basiliximab was used in 49 patients and ATG was used in 23 patients for induction therapy. Eighteen cases had no induction therapy. One case used cyclosporin+ MMF+ prednisolone, one case used everolimus+ prednisolone, and all other patients used tacrolimus+ MMF+ prednisolone for maintenance immunosuppression. Acute rejection was seen in 8 cases and chronic rejection was seen in one case.

According to severity of the cases pulse steroid only (5 cases) or pulse steroid+ ATG (3 cases) were used for acute rejection treatments. A total of 25 patients had ATG for induction or rejection treatment. DGF was seen in 7 patients. During follow up, 2 graft loss cases were seen. All patients had DJS at the time of kidney transplantation operation. ARD-DJS were used in 46 (51%) of the patients. Thirty (33.3%) of the patients had UTI during their posttransplant follow ups. Recurrent UTI was seen in 7 (23.3%) of these cases. Less UTI and recurrent UTI were observed in cases who had ARD-DJS compared to who had St-DJS, but these differences were not statistically significant (P=0.14 and P=0.26 respectively). Five cases (5.5%) had BK viremia. BKN was observed by kidney biopsy in 2 out of 5 cases. All 5 cases with BK viremia were St-DJS users (P=0.025). Of five cases with BKN, viremia was diagnosed at 2nd and 3rd postoperative months in 2 cases, it was diagnosed in one case at 3rd and fourth postoperative months. The other two cases were diagnosed 9 months viremia. Both two cases with biopsy proven BKN had lost their grafts. Basiliximab was used in two cases. Other patient did not receive induction therapy. Median and IQR of the last serum creatine of the patients were 1.00 [0.83-1.28] respectively. Serum creatine did not differ between ARD-DJS and St-DJS groups (P=0.591). There were no urinary leak observed among the patients. But one patient in ARD-DJS group experienced UNS stenosis and had UNS revision operation.

Discussion

For postoperative UTI and postoperative urinary complication risk there were no statistically significant difference between ARD-DJS use and St-DJS use during ureteral anastomosis in 90 kidney transplanted patients who were operated in two centers. BKN univariate analysis were significantly less than those st-DJS used. But significant differences were not logistic regression.

DJS use during kidney transplantation has some advantages such as decreasing ureteral stenosis, obstruction and urinary leak ratios, and has some disadvantages such as stent migration, early UTI, need for a separate urological procedure for removing it [17-21]. Some studies show that DJS use increase BKN risk. Kayler et al used DJS for 49.2% of the 600 kidney transplant patients they report in their study [22]. They found BK viremia in 15.5% of their cases at first year posttransplant. They found a statistically significant association with DJS use and BK viremia by multivariate analysis. Again in the same study 84.9% of the cases were diagnosed as having BK viremia in the first 6 months of transplantation [22]. Hashim et al found in their study with 621 cases that 21.8% of patients with DJS and 16.4% of patients without DJS had BK viremia. But association between BK viremia and DJS were only significant in patients with multiple transplantations [23]. In our study, BK viremia rate was 5.5% in patients. Brennan et al [4] and Thomas et al [12] found in their studies that DJS use increase BKN risk 4.3 and 4.7 fold respectively.

Stent use and BKV association are explained by some theories and supported by some experimental and clinical studies. Stent use may cause superficial epithelial erosion and destruction of ureters and may cause ulceration and reactive changes on transitional epithelium. Also, ureteral reflux that is caused by DJS during ureter contraction may facilitate intrarenal spread of urothelial BKV [13-15]. Absence of BKV in patients with ARD-DJS in our study may support these theories. In a study that investigates ARD-DJS vs St-DJS use and VUR and UTI association, there were no difference in ARD-DJS and St-DJS groups for frequency of VUR and UTI [24]. In our study, we found that frequency of UTI and recurrent UTI were lower in ARD-DJS group, but these differences were not statistically significant (P=0.14 and P=0.26 respectively).

Retrospective nature of the study, absence of non stenting control group were the limited factors for this study. But to the best of our knowledge, despite these limiting factors, this is the

first study that compares ARD-DJS and St-DJS for development of BKN and UTI.

As a result there are many studies that shows DJS use and increased risk of BKN development after kidney transplantations. For postoperative UTI and postoperative urinary complication risk there were no statistically significant difference between ARD-DJS use and St-DJS use during ureteral anastomosis. BKN univariate analysis were significantly less than those st-DJS used. Risc factors (agressive immunosuppression, HLA mismatch, ureteral stent use, rejection and prolonged ischemia time) were evaluated. But results were not statistically significant in the logistic regression analysis. We think that to demonstrate this benefit, we need randomized controlled studies with more patients and longer follow up.

Disclosure of conflict of interest

None.

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