Native Nephrectomy with Renal Transplantation Decreases Hypertension Medication Requirements in Autosomal Dominant Polycystic Kidney Disease

Ashley M Shumate[1*], Clinton D Bahler[1*], William C Goggins[2], Asif A Sharfuddin[3], and Chandru P Sundaram[1]

*Authors contributed equally to manuscript as co-first authors

[1]Department of Urology, Indiana University, Indianapolis, IN, USA

[2]Department of Surgery, Indiana University, Indianapolis, IN, USA

[3]Department of Medicine/Division of Nephrology, Indiana University, Indianapolis, IN, USA

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Corresponding author
Chandru P. Sundaram, MD
Department of Urology, Indiana University
535 N Barnhill Dr., STE 420
Indianapolis, IN 46202
Tel: 3179483098
Fax: 317-944-0174
Email: Sundaram@iupui.edu

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ABSTRACT

Background: In autosomal dominant polycystic kidney disease(ADPKD), hypertension(HTN) is the most prevalent complication and plays an essential role in morbidity and progression of chronic kidney disease(CKD).

Objective: To assess control of HTN following native nephrectomy(Nx) and renal transplant recipients with ADPKD.

Design, Setting, and Participants: Blood pressure control was studied retrospectively in 144 ADPKD patients who underwent renal transplantation between 2003 and 2013.

Intervention: Renal transplantation alone(n=67) versus renal transplantation with concurrent ipsilateral Nx(n=40) versus renal transplantation with concurrent ipsilateral Nx and delayed contralateral nephrectomy(n=37)

Outcome Measurements and Statistical Analysis: The primary outcome was change in quantity and defined daily dose(DDD) of antihypertensive medications after renal transplantation. Predictors of DDD at 36months were assessed using a multivariable linear regression model.

Results and Limitations: Comparing pre-operative to post-operative medications at 12, 24, and 36months follow-up, transplantation with concurrent ipsilateral Nx had a greater decrease in quantity(-1.2 vs -0.5medications, p=0.008; -1.1 vs -0.3, p=0.007; and -1.2 vs -0.4, p=0.03) and DDD(-3.3 vs -1.0, p=0.0008; -2.9 vs -1.0, p=0.006; and -2.7 vs -0.6, p=0.007) of antihypertensives than transplantation alone, respectively. There was a significant decrease in quantity(p=0.0005) and DDD (p=0.009) of medications from post-ipsilateral to 12months post-contralateral Nx. Limitations included retrospective design and inability to correlate blood pressure measurements

with antihypertensive medication changes.

Conclusion: In ADPKD patients undergoing renal transplantation, concurrent ipsilateral native Nx significantly decreases quantity and DDD of antihypertensives. Delayed contralateral native Nx decrease these further.

Patient Summary: We examined blood pressure control following kidney transplantation and removal of native kidneys in autosomal dominant polycystic kidney disease patients. Patients with one native kidney removed at time of transplantation required less blood pressure medications than those who had kidney transplantation alone. Patients who had their second native kidney removed at a later surgery required even fewer medications to control blood pressure.

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease(ADPKD) is one of the most common renal diseases, affecting 1:400 to 1:1000 people. Among its manifestations, hypertension(HTN) stands out as the most prevalent complication, and is an essential component to the development and progression of both renal disease and morbidity and mortality.[1] HTN in ADPKD occurs early, around age 30, and is the initial presentation for approximately 30% of patients.[2] In approximately 60% of patients, HTN occurs before any impairment of renal function.[3] HTN plays an essential role in morbidity of ADPKD, as cardiovascular complications account for the majority of deaths since renal replacement therapies have become prevalent.[4, 5] Therefore, it is crucial to aggressively control HTN to preserve and improve cardiac and renal function.[6]

Once progressive expansion of renal cysts occurs, the massive enlargement of the kidneys and simultaneous shrinkage of normal renal parenchyma eventually leads to renal failure. There is an inverse relationship of renal function and HTN: as renal function declines, the frequency and severity of HTN increases.[7] When end stage renal disease (ESRD) occurs in ADPKD, there is also increased risk of other cardiovascular events.[8] Renal transplantation(Tx) is the treatment of choice for ESRD. Complications after Tx in ADPKD patients are no greater than in the general population.[1] However, despite a functioning renal Tx, the voluminous native kidneys may exert a sustained hypertensive effect. How to properly manage the native kidneys after Tx, and whether or not surgical means are necessary, remains disputed.[9]

Few studies have shown how HTN control is affected with surgical intervention for native cystic kidneys. Native nephrectomy (Nx) is occasionally performed at time of

renal Tx in ADPKD for refractory pain caused by the cumbersome cystic kidney(s), but has not been well-documented as a potential therapy for HTN. The few studies that have examined how Nx affects HTN have been small or only examined blood pressure control in the perioperative period; however, these studies have shown some improvement from Nx.[9-11] No large study has shown significant improvement or resolution of HTN at long-term follow-up for native Nx with renal Tx in the ADPKD population. Our goal was to evaluate how blood pressure responds long-term to this surgical intervention. Our hypothesis was ipsilateral native Nx at time of renal Tx would decrease required antihypertensives to control blood pressure long-term, and that delayed contralateral native Nx would further decrease antihypertensive requirement.

MATERIALS AND METHODS

Population

Our institution's transplant and billing databases were searched for patients who carried a diagnosis of ADPKD and had renal Tx between 2003 and 2013. Patients who had Tx alone or Tx with concurrent ipsilateral native Nx were included. Patients were excluded if they had bilateral Nx at time of Tx(n=9), had multi-organ transplant(e.g. liver and kidney, (n=3), were lost to follow-up(n=14), or were deceased within 4 months of Tx(n=4). 144 patients met the inclusion criteria. Institutional review board approval was obtained for this study.

The primary outcome was change in quantity and defined daily dose of antihypertensive medications for patients after renal Tx. Patients not being treated with antihypertensive medications at the time of transplantation were excluded from the analysis(n=26). Defined daily dose(DDD) is a means of standardizing and analyzing

drug consumption among patients, and was created by the World Health Organization. It is the “assumed average maintenance dose per day for a drug used for its main indication in adults.”[12] Since it can differentiate between different doses of the same medication, DDD provides better representation of drug requirements compared to using the quantity of different medications alone. Patient comorbidities were compared at time of Tx using Charlson Comorbidity Index(CCI).[13] Glomerular filtration rate(GFR) was obtained as an appraisal of renal function, and was calculated using the Modification of Diet in Renal Disease(MDRD) equation.[14] Blood pressure measurements were obtained from clinic notes pre-operatively and through 36 months follow-up. Native Nx at time of renal Tx was performed by the transplant surgeon by an open approach, and the completion native Nx was performed by a urologic surgeon using a laparoscopic approach at a mean of 9.8 months post-Tx. Details of the surgical procedures have been described previously.[15] The standard immunosuppression regimen was early steroid withdrawal(<7 days), and maintenance immunosuppression with tacrolimus and mycophenolate.

Statistical analysis

Descriptive analysis was performed for demographic data. Student’s T-test was used for continuous variables and Pearson chi-square test for categorical variables. A 2-tailed analysis was performed in all tests. Comparing antihypertensives between post-first Nx and post-second Nx was done using a paired Student’s T-test. All other analyses were un-paired. The analysis of variance(ANOVA) test was used for GFR at 12, 24, and 36-months postoperatively. Multivariable linear regression was used to determine predictors of DDD of antihypertensives at 36 months. Age, CCI, tobacco use,

and BMI were included in the multivariable analysis *a priori* as they were identified as potential confounders. Nephrectomy status and gender were included in the multivariable analysis due to having a *p-value* <0.05 on univariable analysis. *A priori* significance was set at p<0.05 for all analyses. All statistical analyses were performed using Stata 13.1(Stata Corp. LP, College Station, TX).

RESULTS

Demographic and patient characteristics data can be found in Table 1. At time of Tx, there was no difference between renal Tx alone(Group 1) vs renal Tx with native Nx(Group 2) in mean age, gender, ethnicity, BMI, percentage of patients with diabetes mellitus, percentage of tobacco users, or percentage of patients requiring pre-Tx dialysis. Similarly, no difference was found between groups in number of patients who carried a diagnosis of HTN at Tx. Mean CCI, international ionized ratio, GFR, and albumin were similar between groups at time of Tx. Hemoglobin at time of Tx was slightly lower in Group 1(12.2 g/dL) compared to Group 2(12.8 g/dL),(p=0.02).

A comparison of medication requirements between Groups 1 and 2 can be found in Table 2. At time of Tx, quantity of medications was similar between Group 1 and Group 2 (2.3 vs 2.6, p=0.23). There was no difference in DDD between Groups 1 and 2 (3.7 vs 4.4, p=0.27) at time of Tx.

Results of medication requirements after ipsilateral and delayed contralateral nephrectomy can be found in Figures 1 and 2. At 4 months post-Tx, the mean quantity of medications required to control blood pressure was significantly less in Group 2 compared to Group 1 (1.3 vs 1.9, p=0.001). Similarly, DDD of antihypertensives was much lower in Group 2 than Group 1 (1.2 vs 2.7, p<0.0001). Similar to 4 months follow-

up, patients in Group 2 required less quantity of antihypertensives and DDD compared to Group 1 at 8, 12, and 24 months follow-up.. At 36 months, while there was a smaller quantity and DDD of antihypertensives in Group 2, this was only significant in DDD of antihypertensives (p=0.003), not quantity(p=0.16).

The mean change in quantity as well as mean change in DDD of antihypertensives was calculated from time of Tx to 12 and 24 months post-Tx for Group 2. These results showed a significant reduction from pre- to post-Tx in quantity and DDD of medications at both time intervals(p=0.008 for change in quantity of medications at 12 months, p=0.007 at 24 months; p=0.0008 for change in DDD of antihypertensives at 12 months, and p=0.006 at 24 months). The association continued up to 36 months follow-up(p=0.03 for quantity of medications, p=0.007 for DDD).

Patients from Group 2 were further subdivided into those who only had single ipsilateral native Nx(Group 2a, n=40) and those who went on to have a delayed contralateral (staged bilateral) native Nx(Group 2b, n=37). Results for Group 2b can be found in Table 3. We compared the antihypertensive requirements from Group 2b before and after their second, contralateral Nx. At 12 months follow-up from their contralateral Nx, the mean quantity of medications decreased from 1.7 to 1.1(p=0.0005) and DDD decreased from 1.4 to 0.8(p=0.009).

Multivariable predictors of DDD of antihypertensives at 36 months can be found in Table 4. Male gender(**β**=1.2, p=0.003), ipsilateral Nx(**β**=-1.6, p=0.004), and bilateral (staged) Nx(**β**=-1.7, p=0.001) were all predictors on multivariable analysis. The multivariable linear regression model was statistically significant($p<0.001$) with $R^2=0.27$.

Reason for native Nx was evaluated and can be found in Table 5. The most

common reason for both first and second native Nx was intractable pain/discomfort. Cyst hemorrhage was the second most common reason. Reason was not specified in 12(15.6%) patients for the first Nx and 6(16.2%) patients for the second, contralateral Nx.

Mean pre-operative blood pressure was similar(p=0.66) among Group 1 (131/77), Group 2a (130/79), and Group 2b (134/80). Mean blood pressures remained similar(p=0.65) among Groups 1 (129/76), 2a (130/79), and 2b (126/75) at 12 months post-operatively. At 24 and 36 months, blood pressures remained similar(p=0.88 and 0.96) between Groups 1 (135/77 and 127/73), 2a (133/76 and 128/73), and 2b (134/76 and 127/74), respectively.

GFR at 12 months was 51 for Group 1, 53.2 for Group 2a, and 60.7 for Group 2b(p=0.02). GFR at 24 months was 53.2 for Group 1, 53.4 for Group 2a, and 54.6 for Group 2b(p=0.94). GFR at 36 months was 53.2 for Group 1, 53.8 for Group 2a, and 53.4 for Group 2b(p=0.90).

DISCUSSION

Our results show ipsilateral native Nx with concurrent renal Tx decreases quantity and DDD of antihypertensive medications as assessed from 4months up to 36months. In addition, patients who had staged bilateral native Nx had a greater degree of decrease in their antihypertensives(Figures 1 and 2). This association persisted on multivariable regression analysis(Table 4) with the presence of Nx having the largest overall effect on decrease in DDD of antihypertensive requirements, with bilateral(staged) Nx having more effect on decrease of DDD than ipsilateral Nx. We did find male gender was predictive of greater DDD of antihypertensives on multivariable

regression analysis, which is consistent with previous studies showing male gender as a risk factor for HTN in this population.[8] We found a decrease in quantity and DDD of antihypertensives in the group who had renal Tx alone, although this decrease was significantly less than that in the Tx/Nx group.

Studies have shown the general population with ESRD who undergo renal Tx typically do not have significant improvement in HTN, but instead frequently(70-90%) develop HTN. More importantly, there have been previous studies showing ADPKD patients experience HTN post-renal Tx at a similar rate to that of the general population.[16, 17] Our findings are novel and contradictory to these other studies that have examined this intervention. However, many of these studies in the past have used steroid maintenance as part of immunosuppression, which contributes to HTN, unlike our patient population who were steroid free.

There are, however, a few, very small studies which have examined a similar surgical intervention of native Nx at time of renal Tx for ADPKD patients. A study by Song et al. showed greater persistence of HTN following Tx alone than with Tx and bilateral native Nx. This study had 24 patients in each group and did not specify follow-up time.[11] Another study also evaluated the effects on HTN of staged native Nx, although this operation was after, not at time of, renal Tx in ADPKD patients. Only one patient in this study had this specific intervention, but it was reported the patient's HTN improved after unilateral Nx and completely resolved after staged bilateral native Nx.[10] Our results support these small studies and to our knowledge are from the largest study to show benefit from surgical intervention of native Nx with renal Tx for HTN control.

The control of HTN in ADPKD is crucial, as these patients are at increased risk for cardiovascular complications leading to morbidity and mortality. In order to avoid such complications, it is recommended ADPKD patients be monitored early and often, looking for elevations in blood pressure. The goal for blood pressure ranges from < 140/90 to <130/80mmHg.[18, 19] Aggressive control is warranted to prevent damage and resultant complications. If multi-drug therapy fails to control HTN, other options, such as nephrectomy, should be considered.

Standard reasons for native Nx in ADPKD patients currently include refractory pain, recurrent infections, refractory hematuria, inadequate space for renal grafts, and dyspnea.[20] Nephrectomies were performed in our patient population for similar reasons. Currently, HTN is not a standard indication for Nx at time of Tx because of lack of previous data demonstrating its benefit. Future randomized studies should assess the benefit of native Nx with renal Tx as a possible treatment for HTN in ADPKD.

Although we demonstrated a decrease in antihypertensive medications needed to control HTN, we cannot conclude with certainty this will lead to decreased complications from HTN for our patient population. Better demonstration of decreased morbidity/mortality could be achieved by following our patient population farther out and comparing cardiovascular complications, such as myocardial infarcts and cerebrovascular attacks, between groups.

There were no differences in clinic-recorded blood pressures during the 36 month follow-up among groups. Although we expected to see a decrease in actual blood pressure to support a decrease in antihypertensives, we do not know exact dates

of medication changes. As such, medications may have been changed based on blood pressure recordings or side effects that were not available during retrospective review.

Our study was not without limitations. We examined patients and medications as part of a retrospective study, and thus there is risk of confounders and bias. A future prospective study could better quantify risk reduction of antihypertensive medications and HTN control after native Nx and Tx. By measuring quantity and DDD of antihypertensives to assess HTN control in our groups, we indirectly examined the control of HTN in our ADPKD patients. To get a truly representative measure of blood pressure control, the addition of home monitoring of daily blood pressures by patients could give a more accurate representation of control. This would best be done in a prospective study. We only examined patients who had ipsilateral Nx at time of Tx. It would be of benefit to examine how bilateral native Nx at time of renal Tx affects blood pressure control, and to see if results are consistent with those of the staged Nx group, or if simultaneous bilateral Nx has a synergistic effect. Safety of the procedure, especially when performed by experienced surgeons, has been well-demonstrated by previous studies.[15, 20-22]

CONCLUSIONS

Ipsilateral native nephrectomy performed at time of renal transplantation significantly reduces the quantity and defined daily dose of antihypertensives needed to adequately control hypertension in patients with autosomal dominant polycystic kidney disease, and staged contralateral native nephrectomy reduces antihypertensive requirement even further. Performing ipsilateral native nephrectomy with renal transplantation and delayed contralateral native nephrectomy on this patient population

with medically-resistant hypertension may provide a surgical means for improved hypertension control.

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Table 1: Demographics and patient characteristics

	Group1 mean (SD)	**Group 2 mean (SD)**	**TOTAL mean (SD)**	***p-value***
n	67	77	144	
Age (years)	54.8 (9.4)	52.7 (10.3)	53.7 (9.89)	*0.20*
Gender Male, no. (%) Female, no. (%)	 30 (45) 37 (55)	 44 (57) 33 (43)	 74 (51) 70 (49)	*0.14*
Race Caucasian, no. (%) Other, no. (%)	 63 (94) 4 (6)	 75 (97) 2 (3)	 138 (96) 6 (4)	*0.46*
Requiring Dialysis Prior to Tx, no. (%)	43 (65)	43 (57)	86 (61)	*0.34*
CCI prior to Tx	2.2 (0.41)	2.1 (0.29)	2.1 (0.35)	*0.21*
DM, no. (%)	2 (3)	4 (5)	6 (4)	*0.51*
BMI prior to Tx (kg/m^2)	27.9 (4.8)	30.8 (17.4)	29.4 (13.2)	*0.20*
Tobacco use, no. (%)	2 (3)	8 (11)	10 (7)	*0.09*
GFR at Tx	8.5 (4.6)	7.5 (4.2)	8.0 (4.4)	*0.19*
Hgb at Tx (gm/dL)	12.2 (1.8)	12.8 (1.7)	12.5 (1.8)	*0.02*
INR at Tx	1.1 (.34)	1.2 (1.0)	1.2 (0.80)	*0.51*
Albumin at Tx (gm/dL)	3.7 (0.41)	3.7 (0.52)	3.7 (0.47)	*0.81*
HTN, no. (%)	54 (80.6)	64 (83.1)	118 (81.9)	*0.70*

no.- number, Nx- Nephrectomy, Tx- Transplantation, BMI- body mass index, GFR- glomerular filtration rate, INR- international normalized ratio, HTN- hypertension

Table 2: Results

	Group 1 mean (SD)	**Group 2 mean (SD)**	**TOTAL mean (SD)**	***p-value***
PreTx quantity of meds	2.3 (1.3)	2.6 (1.2)	2.5 (1.2)	*0.23*
Number of patients	54	74	118	
PreTx DDD of meds	3.7 (3.1)	4.4 (3.4)	4.1 (3.3)	*0.27*
Number of patients	51	61	112	
DDD of meds at 4 mo	2.7 (2.1)	1.2 (1.5)	1.9 (2.0)	*<0.0001*
Number of patients	54	64	118	
Quantity of meds at 4 mo	1.9 (1.1)	1.3 (1.0)	1.6 (1.1)	*0.001*
Number of patients	54	64	118	
DDD of meds at 8 mo	2.8 (2.2)	1.0 (1.1)	1.9 (2.0)	*<0.0001*
Number of patients	54	52	106	
Quantity of meds at 8 mo	1.9 (1.1)	1.3 (0.9)	1.6 (1.0)	*0.002*
Number of patients	54	52	106	
DDD of meds at 12 mo	2.7 (2.3)	1.0 (1.2)	2.0 (2.1)	*0.0001*
Number of patients	54	42	96	
Quantity of meds at 12 mo	1.9 (1.1)	1.3 (0.9)	1.6 (1.1)	*0.019*
Number of patients	54	42	96	
DDD of meds at 24 mo	2.7 (2.2)	1.3 (1.5)	2.1 (2.1)	*0.002*
Number of patients	54	33	87	
Quantity of meds at 24 mo	2.0 (1.2)	1.5 (1.0)	1.8 (1.1)	*0.045*
Number of patients	54	33	87	
DDD of meds at 36 mo	2.9 (2.3)	1.4 (1.4)	2.4 (2.1)	*0.003*
Number of patients	47	26	73	

Quantity of meds at 36 mo	2.0 (1.2)	1.6 (0.9)	1.8 (1.1)	*0.16*
Number of patients	47	26	73	
Change in mean quantity of meds from preTx to 12 mo	-0.5 (1.5)	-1.2 (1.3)	-0.8 (1.4)	*0.008*
Change in DDD from preTx to 12 mo	-1.0 (3.0)	-3.3 (3.3)	-2.0 (3.3)	*0.0008*
Change in mean quantity of meds from preTx to 24 mo	-0.3 (1.4)	-1.1 (1.1)	-0.6 (1.3)	*0.007*
Change in DDD from preTx to 24 mo	-1.0 (2.9)	-2.9 (1.7)	-1.7 (3.0)	*0.006*
Change in mean quantity of meds from preTx to 36 mo	-0.4 (1.5)	-1.2 (1.4)	-0.6 (1.5)	*0.03*
Change in DDD from preTx to 36 mo	-0.6 (3.1)	-2.7 (2.8)	-1.3 (3.1)	*0.007*

Tx-transplantation, mo-months, DDD-defined daily dose

Table 3. Results of Staged Nephrectomy (Group 2b)

	Group 2b before 2nd Nx	Group 2b after 2nd Nx	p-value
Quantity of meds, pre-2nd Nx to 12 mo follow-up	1.7 (0.7) before	1.1 (0.7) after	0.0005
DDD of meds, pre-2nd Nx to 12 mo follow-up	1.4 (1.3)	0.8 (0.9)	0.009

Nx-Nephrectomy, meds-medications, mo-months, f/u-follow-up, DDD-defined daily dose

Table 4. Multivariable predictors of 36-month defined daily dose (DDD) of hypertensive medications

	β	p-value	95% Confidence Interval	
Nephrectomy (reference=none)				
Ipsilateral Nx	-1.6	0.004	-2.64	-0.53

Bilateral Nx	-1.7	0.001	-2.70	-0.74
Gender (male)	1.2	0.003	0.42	2.04
Age	0.0	0.375	-0.02	0.06
Tobacco use	-0.5	0.523	-2.03	1.04
CCI	0.2	0.753	-0.99	1.36
BMI	0.0	0.922	-0.7	0.08

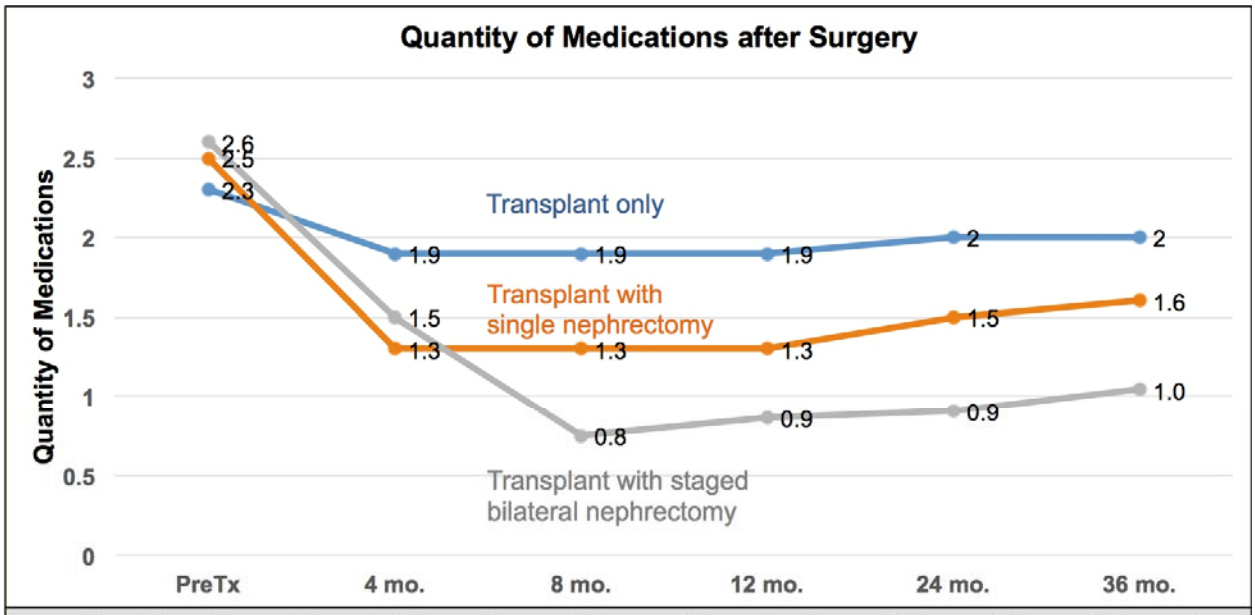
CCI- Charlson comorbidity index, BMI-body mass index, Nx-nephrectomy

Table 5. Reason for Native Nephrectomy

Reason for Nephrectomy	Nephrectomy 1 no. (%)	Nephrectomy 2 no. (%)
Pain/Discomfort	54 (70)	28 (75.7)
Dyspnea	1 (1.3)	1 (2.7)
Early Satiety	2 (2.6)	0 (0)
Cyst Hemorrhage	6 (7.8)	2 (5.4)
Recurrent UTI	1 (1.3)	0 (0)
Rule out RCC	1 (1.3)	0 (0)
Reason not specified	12 (15.6)	6 (16.2)

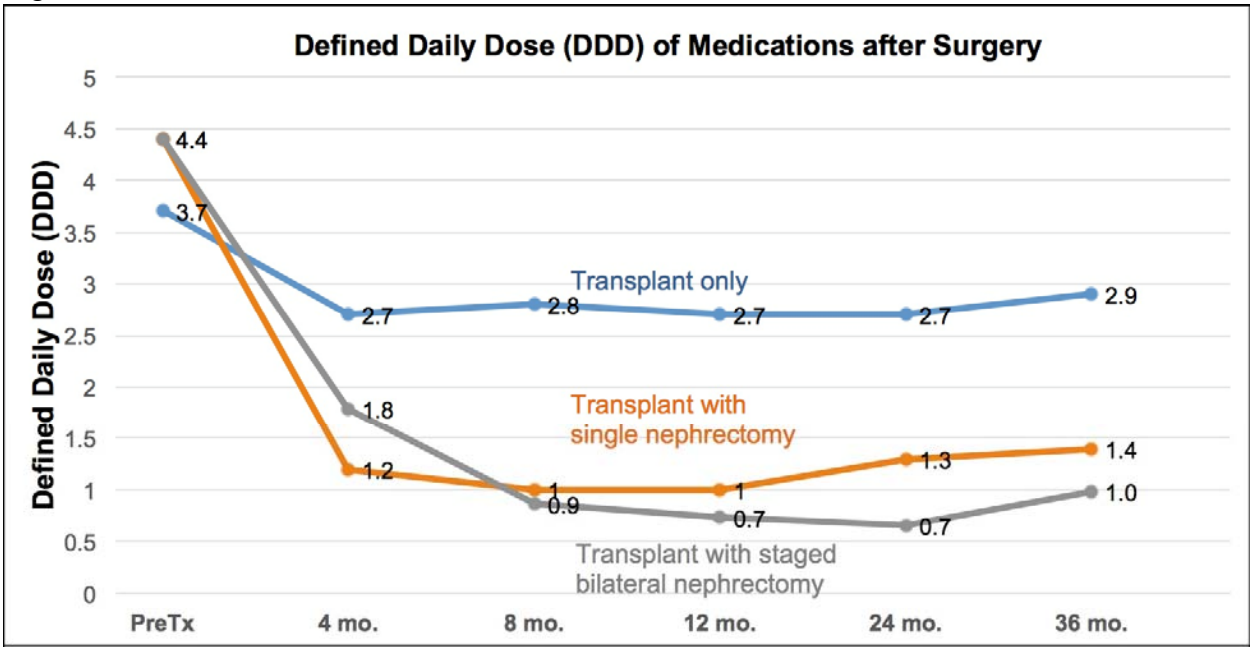
no.-number, UTI-urinary tract infection, RCC-renal cell carcinoma

Figure 1



	PreTx (n)	4 mo (n)	8 mo (n)	12 mo (n)	24 mo (n)	36 mo (n)
None	54	54	54	54	54	47
Nx	64	54	52	42	33	26
2nd Nx		4	12	22	21	24
P-value	*0.63*	*0.003*	*<0.001*	*<0.001*	*<0.001*	*0.003*

Figure 2



	PreTx (n)	4 mo (n)	8 mo (n)	12 mo (n)	24 mo (n)	36 mo (n)
None	51	54	54	54	54	47
Nx	61	64	52	42	33	26
2nd Nx		4	12	22	21	24
P-value	*0.56*	*<0.001*	*<0.001*	*< 0.001*	*<0.001*	*<0.001*