Early Postoperative Urine Flow Predicts Delayed Graft Function Irrespective of Diuretic Use

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ABSTRACT

Delayed graft function (DGF), a manifestation of ischemic/reperfusion injury, is detrimental to allograft survival. Urine flow may predict development of delayed graft function. Intraoperative frusemide during cadaveric renal transplantation may reduce DGF. We performed a retrospective analysis of consecutive renal transplants over a 3-year period. Patients received frusemide or no diuretic intraoperatively. Allograft function postoperatively was determined by a 10% fall in serum creatinine in the first 24 hours or need for dialysis in the first week.

Of the 99 patients in the study group, 57 patients received frusemide (Group A) and 42 patients received no diuretic (Group B). Thirty % of Group A patients and 31% of Group B patients had DGF. Fourteen patients in Group A and 12 patients in Group B required dialysis post-transplantation respectively. Cold ischemic times between groups were similar (P>0.2). Poor urine flow post-ureteric anastomosis was more frequent in Group B (4 versus 12). Eighteen of 19 patients who had passed less than 1 liter of urine in the first 24 hours developed DGF. Serum creatinine at 3, 6, and 12 months post-transplantation were not significantly different between the groups (P=0.15, 0.1, and 0.6). Patients with DGF irrespective of frusemide administration had significantly higher creatinine values throughout (P<0.01).

All recipients had negative cross-matches and 60% and 71% had 3 HLA matches. Mean donor ages were similar between groups (P=0.34). Underlying hypertension was more common in the donors for Group A (35% versus 19%) but terminal serum creatinines were similar (86.5±.7 versus 88.3±4.0 μmol/L). Atheroma in the donor renal artery or attached aortic patch was present in 37% of Group A patients and 31% of Group B cases.

In this limited study, frusemide

Table 1. Causes of End Stage Renal Disease in Patient Population Undergoing Cadaveric Renal Transplantation

Cause Of End Stage Renal Disease	Frusemide Group (A)	No frusemide group (B)
Alports syndrome	1	1
Diabetic nephropathy	4	0
Mesangio capillary glomerulonephritis	2	3
Hypertension	3	3
Lupus/vasculitis	1	2
Rapidly progressive glomerulonephritis	3	1
Membranous	1	2
Polycystic kidney disease	8	7
IgA nephropathy	11	4
Glomerulonephritis (unspecified)	3	5
Chronic glomerulonephritis	1	0
Analgesic nephropathy	1	3
Interstitial nephritis	0	2
Reflux disease	3	1
Dysplastic kidney disease	0	2
Focal and segmental glomerulosclerosis	3	3

appears to have no effect on DGF. Patients passing less than 200 mL of urine within the first 4 hours are likely to have DGF irrespective of frusemide administration.

INTRODUCTION

Delayed graft function (DGF), an entity thought to be the principal manifestation of ischemic/reperfusion injury, is detrimental to both early and late allograft survival.[1-4] DGF may also represent a degree of immunological insult on the transplanted kidney. Ischemic injury is also related to cold ischemic time and donor factors. Intraoperative frusemide during cadaveric renal transplantation may improve the rates of early graft function.[5] Frusemide may potentially limit the degree of tubular damage related to ischemic injury. However, there is little data in the literature as to the use of frusemide intraoperatively during cadaveric renal allograft transplantation. Frusemide is used in the study authors unit according to surgeon preference. We therefore carried out a retrospective analysis of consecutive cadaveric renal transplants performed in a single center over a 3-year period (1998-2000).

METHODS

All cadaveric transplants in the previous 3 years were examined. Live related and live unrelated transplants were excluded from the study. Two urologists, who alternated on the cadaveric transplant surgical roster, were involved; only one of whom uses intraoperative frusemide. Warm ischemic times and operative times were similar in the 2 groups. Patients therefore received either intravenous frusemide or no diuretic therapy during completion of the ureteric anastomosis intraoperatively. Postoperatively patients were optimally hydrated maintaining a central venous pressure of greater than 8 mmHg. Renal allograft

Table 2. Complications Occurring in the First Week Post-cadaveric Renal Transplantation

Complications	Frusemide group (A)	No frusemide group (B)
None	37	20
Ureteric spasm	3	1
Hematuria/clots	3	2
Wound hematoma	3	2
Wound infection/breakdown	9	10
Urinary retention	1	1
Arterial bleed	1	0
Bladder leak	0	1
Other	1	2

function was assessed by a spontaneous fall in serum creatinine of at least 10 % in the first 24 hours of the postoperative period. Requirement for dialysis post-surgery or in the first week post-transplantation was considered due to a delay in graft function, unless it was purely for treatment of hyperkalemia. Donor details were recorded on all patients. All patients received standard protocol doses of prednisone and cyclosporin at induction and 1 other immunosuppressive agent (azathioprine, mycophenolate mofetil or rapamycin) on the day of surgery.

Data are given as mean results ± the standard error of the mean (SEM), with median values or ranges given in brackets. Significance was calculated at the 0.05 level using Student *t* test analysis.

RESULTS

A total of 57 patients (18 female and 39 male, mean age 47.9±1.8 years [median 47 years]) received intravenous frusemide. The remaining 42 patients (21 male and 21 female, mean age 44.9±1.9 years [median 44.5 years]) received no diuretic treatment. Causes of end stage renal disease are detailed in Table 1. Post-transplantation complications were similar in both groups (Table 2). In the frusemide group, after one year there had been 3 deaths and 1 patient returning to dialysis, while in the non frusemide group there had been 1 death. Seventy % of the frusemide group and 69% of the no frusemide group had no delay in graft function. A total of 26 patients (26.3%) required dialysis post-transplantation for DGF (14, Group A; 12 , Group B). Two other patients, 1 in each group, required a single dialysis session post-transplantation for treatment of hyperkalemia only, despite a significant spontaneous fall in serum creatinine. These were considered not to be a delay in graft function. There were 2 patients with diabetes in the frusemide group and 1 in the other group. Subgrouping patients according to a delay in graft function and whether they received frusemide or not demonstrated no significant difference in cold ischemic times between the 4 subgroups ($P>0.2$, Table 3). However serum creatinine at 3, 6, and 12 months post-transplantation was significantly higher in those patients with delayed graft function (3 months, 123.7±4.9 versus 177.6±18.5, $P=0.0024$; 6 months, 124.6±4.9 in comparison to those without DGF 171.9±21.1, $P=0.0036$; 12 months, 127.3±5.1 versus 169.4±18.1, $P=0.004$).

Serum creatinine values at the following intervals between Groups A and B respectively were: 3 months (Group A, 138.6±9.7 µmol/L; Group B, 141.5±9.6 µmol/L; $P=0.15$), 6 months (Group A,139.6±12 µmol/L; Group B, 139.1±8 µmol/L; $P=0.1$) and 12 months (Group A,140.8±11 µmol/L; Group B, 140.1±7

Table 3. Ischemic Time and Serum Creatinine Values in Study Patients With/Without Frusemide

	Graft Function	Ischemic Time (hours)	No. of patients	Creatinine (µmd/L) 3/12	Creatinine (µmd/L) 6/12	Creatinine (µmd/L) 12/12
Frusemide	No delay	15.6±0.8	40	123.7±6.6	121.6±5.8	128.1±7.5
	Delay	18.2±1.4	17	173.7±27.4	178.7±34.9	168±30.6
No Frusemide	No delay	15.2±.0.78	29	123.6±7.2	128.9±8.7	126.2±6.7
	Delay	16.9±0.9	13	183.3±23.5	162.2±12.9	171.4±13.3

Table 4. HLA and Subgroup DR Matches in Frusemide and No Frusemide Groups Undergoing Cadaveric Renal Transplantation.

HLA matches out of a total of 6/6	Frusemide group (A)	No frusemide group (B)
0	6	2
1	3	5
2	14	5
3	18	11
4	6	13
5	6	3
6	4	3
<3/6	23	12
≥3/6	34	30
DR matches out of a total of 2/2		
0	12	7
1	11	7
2	34	28

µmol/L; *P*=0.5). The values were also not significantly different. No adverse effects were noted in the frusemide group as a result of its administration.

In Group A, 4 patients had no urine flow, during the operation after ureteric anastomosis was complete; 3 of whom went on to develop DGF. By 4 hours postoperatively, 5 patients had passed less than 200 mL of urine; all of these patients went on to develop DGF. At day of transplantation, 9 patients had passed less than 1 liter of urine; 8 of whom had DGF.

In Group B, 12 patients had no urine flow during surgery after ureteric anastomosis and 6 of these patients developed DGF. By 4 hours post-surgery, 9 patients had passed less than 200 mL of urine; all these patients went on to developDGF. At day of transplantation, 10 patients had passed less than 1 liter of urine; all of whom had DGF. Postoperative complications were similar in both groups and mainly surgically related (Table 3).

HLA matching at transplantation (Table 4) showed that 59.6 % (Group A) and 71.4 % (Group B) had a 3 or greater HLA match and 79% (Group A) and 83.3% (Group B) had at least 1 DR match. All recipients had negative T and B cell crossmatches and 89.5% (Group A) and 90.5% (Group B) had antibody titers of less that 30 % (Table 5).

Examination of donor factors gave a mean donor age of 41.7±2.3 years (26 female and 31 male, median age 48 years) in Group A and 44.8+2.3 years (15 female and 27 male, median age 46.5 years) in Group B (*P*=0.34). The major-

Table 5. Antibody Titers and Crossmatch Details for Cadaveric Renal Transplants in Comparison to Recipients

	Frusemide group (A)	No frusemide group (B)
Peak < 30%	37	26
Peak 30-50%	6	6
Peak >50%	14	10
Current <30%	51	38
Current 30-50%	3	4
Current >50%	3	0
Crossmatch	All negative	All negative

Table 6. Donor Details

Cause of death	**Frusemide group (A)**	**No frusemide group (B)**
MVA/trauma/injury	19	18
Cerebrovascular event	12	7
SAH/ICH	23	15
Other	3	2
Donor characteristics	**Frusemide group (A)**	**No frusemide group (A)**
Presence of vascular disease	10	4
Presence of hypertension	20	8
Atheroma in renal/aorta	Mild 7	Mild 2
	Moderate/severe 14	Moderate/severe 11

ity of kidneys came from donors who died from trauma/motor vehicle accident (MVA), a stroke or an intracranial hemorrhage (Table 6). There was an excess of donor cases with underlying hypertension in Group A, 35.1 % versus 19 % in Group B. However serum creatinine levels at the time of death were similar (88.3±4 μmol/L in Group A versus 86.9±4.7 μmol/L in Group B, [P=0.46]). Atheroma in the renal artery or attached aortic patch was present at surgery in 36.7% of cases in Group A and 31 % of cases in Group B.

DISCUSSION

Hypoxic injury is a major cause of tubular necrosis in the corticomedullary junction and may be ameliorated by inhibitors of active reabsorption, such as frusemide. In animal models, frusemide infusion stimulates a significant effect on cortical hemoglobin oxygenation in transplanted kidneys and on active reabsorption in the corticomedullary junction.[5] In cadaveric kidney transplantation, post-transplant acute renal failure was shown to be reduced by more than 50% in those kidneys protected with frusemide and methylprednisolone.[6] These kidneys however were preserved by a combination of topical hypothermia and pulsatile perfusion with cryoprecipitate plasma. From these previous findings, perhaps, one can postulate that frusemide given early in transplantation may reduce DGF.

Although there is limited data, frusemide is frequently used intraoperatively to putatively improve early graft function. This present data suggests that frusemide does not appear to reduce the delay in allograft function during the early postoperative period. Although 21.5% of patients not receiving diuretic passed less than 200 mL of urine by 4

Table 7. Urine Output in Early Postoperative Period

Urine output	Frusemide group (A)		No frusemide group (B)	
	No DGF	DGF	No DGF	DGF
During operation	6	6	1	3
Within 4 hours <200 mL of urine	0	9	0	5
Day zero <1 L	0	10	1	8

hours in comparison to 8.7% of those receiving frusemide; by day one, 23.8% of the frusemide group and 15.7% of the no frusemide group passed less than 1 liter of urine. Clearly, urine flow may help predict delayed graft function irrespective of diuretic use as no patient who passed more than 200 mL by 4 hours developed DGF (Table 7). Indeed those who develop DGF are more likely to have worse function at 1-year post-transplantation. This data should be viewed with caution; the number of patients examined is somewhat small to provide sufficient statistical power. Large doses of diuretic may not have produced the desired effect and bias potentially exists from the surgeons, who may be partly responsible for the quality of immediate outcome.

Although both recipient groups were similar, the donor groups were somewhat different. The overall mean donor age was 41.7±2.3 in the frusemide group and 44.8±2.3 years in the no frusemide group. Of the combined groups 28.3% had a history of hypertension and approximately 34.3 % of donors had evidence of atheroma affecting either the renal artery of adjacent aorta. More donors in the frusemide group had vascular disease. Clearly donor factors are important determinants of immediate transplant function and outcome.[7,8] In particular, there is a strong relationship to ischemic injury. Indeed, explosive brain death in experimental models has been shown to produce release of cytokines and renal inflammation,[9] which may be detrimental to transplant function after transplantation. However both of our groups were from donors with similar causes of death. The short-term outcome in this study, in terms of graft function is statistically similar for both groups. Delayed graft function is associated with poor renal outcome with a 19% lower 1-year graft survival[4] as also noted in this study.

CONCLUSION

This present study suggests that perhaps frusemide given early in cadaveric renal transplantation may be of little clinical benefit during intraoperative administration on DGF. However, frusemide may help surgeons confirm successful renal perfusion, if urine is seen coming from the transplant ureteric orifice prior to anastomosis. Patients passing less than 200 mL of urine within the first 4 hours after surgery are likely to have DGF irrespective of frusemide administration and subsequently, may require a period of dialysis therapy. Donor factors and cold ischemic time may ultimately influence the outcome of cadaveric renal transplantation, and perhaps, the aim should be to optimize renal perfusion prior to donor harvest and limit the inflammatory response of the donor kidney.

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