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Original Research

Outcome of renal transplantation with and without intra-operative diuretics

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ABSTRACT

Aims: This paper presents an e-survey of current clinical practice of use of intra-operative diuretics during renal transplantation in the United Kingdom and a study to compare outcome of renal transplants carried out with or without intra-operative diuretics in our centre.

Methods: An e-mail questionnaire to renal transplant surgeons exploring their practice of renal transplantation with or without intra-operative diuretics, the type of a diuretic/s if used and the relevant doses. An observational study comparing the outcome of renal transplant recipients, group no-diuretics (GND, $n = 80$) carried out from 2004 to 2008 versus group diuretics (GD $n = 69$) renal transplant recipients who received intra-operative diuretics over a one year period is presented. Outcome measures were incidence of delayed graft function and a comparison of graft survival in both groups.

Results: Forty surgeons answered from 18 transplant centres with a response rate of 67%. 13 surgeons do not use diuretics. Mannitol is used by 10/40, Furosemide 6/40 and 11 surgeons use a combination of both. In comparative study there was no significant overall difference in one year graft survival of GD versus GND ($N = 65/69$, 94% and 75/80, 94% respectively, $p = 0.08$) and the incidence of delayed graft function was also comparable (16/69, 23% and 21/80, 26% respectively, $p = 0.07$). The donor characteristics in both groups were comparable.

Conclusion: The study showed variation in clinical practice on the use of intra-operative diuretics in renal transplantation and it did not demonstrate that the use of diuretics can improve renal graft survival.

1. Introduction

The term Delayed graft function (DGF) is controversial and most commonly used for lack of acceptable renal function requiring dialysis in one week after transplantation.[1] DGF does not occur after all renal transplantations; there is a wide variation in reporting (5–93%) depending on the source of the graft,[2,3] but most centres report a DGF rate of 20–40%.[4] However the term DGF remains vague and there are a number of criterion and definitions described for DGF. Factors associated with an increased occurrence of DGF can be categorised in to three areas, i.e. donor, recipient and transplant procedure.[5] Donor factors include: increased age, hypertension (>10 years), creatinine clearance <80 mL/min, vascular sclerosis, weight, female gender, and atraumatic death. Recipient factors are pre-sensitization, ethnicity, pre-transplant levels of proinflammatory cytokines, pre-transplant anuria, pre-transplant mean arterial pressure (<100 mmHg), and American Society of Anesthesiologists physical status category IV (a patient with an incapacitating systemic disease that is a constant threat to life). Transplant procedural factors comprise cold ischemia time, warm ischemia time, anastomotic time, and selection of preservation solution.[5]

One important co-existing or contributory factor to DGF which can delay the primary function of the transplanted kidney is acute tubular necrosis. The incidence of post operative acute tubular necrosis (ATN) after cadaveric kidney transplantation has been reported in the literature to vary from 30 to 60%.[6–9] There is controversy about the influence of ATN on the ultimate fate of the graft.[9] In a study of 354 transplantations performed in Nijmegen, incidence of ATN of 42% was reported with a significant negative influence on graft survival. Apart from its possible adverse effect on graft survival it is important to prevent ATN because it hampers the diagnosis of early rejection, increases the necessity of diagnostic procedures (radionuclide scans, echography, and transplant biopsies), and introduces dialysis-associated morbidity. Traditional strategy to prevent ATN is the use of adequate hydration in combination with diuretics during renal implantation. The haemodynamic condition of the donor prior to nephrectomy and the length of initial warm ischemia time have been considered major determinants in the development of ATN after surgery.[10] However, a number of recent studies have indicated that the haemodynamic parameters of the recipient during the transplantation procedure are of even greater importance. Luciani et al.[11] and Carlier et al.[12] were able to

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reduce the incidence of ATN to 11% and six per cent, respectively, by maximal hydration of the recipient during the operative procedure. However the evidence to support the use of diuretics in order to prevent ATN is scarce and anecdotal.[13] This paper presents a sequential study on the use of intra-operative diuretics in renal transplantation. The study describes a survey of the use of diuretics in various transplant centres in the United Kingdom. It is followed by an analysis of the outcome of renal transplants carried out without any intra-operative diuretics in our centre and their comparison with a cohort of patients who received diuretics during surgery.

2. Methods

An e-mail questionnaire was circulated to renal transplant surgeons in various transplant centres in the United Kingdom. It was a 4 item questionnaire to explore the personal practice of renal transplant surgeons about the use of intra-operative diuretics during kidney implantation. The questions asked were aimed to explore the use of any intra-operative diuretics/combination of diuretics or no diuretics during renal transplantation and their doses used.

Delayed graft function was defined as requirement of dialysis within one week after transplantation for reasons other than hyperkalaemia or fluid overload. A retrospective analysis of the outcome of those patients ($N = 80$) who were not given any intra-operative diuretics during renal transplantation in a five year period (2004–2008) in our centre was carried out (Group non- diuretics, GND). The outcome of GND was then compared with those 69 transplants who were given diuretics (Group diuretics, GD), carried out over a period of one year in our centre, March 2008 to February 2009. The choice of diuretics or none was individual surgeon's policy and was consistent in all cases performed by the same surgeon. All renal transplantations were carried out under the supervision of consultant surgeons by using retroperitonal approach. All transplants carried out from 2006 onwards received same immunosuppression regimens including a combination of Prednisolone, Tacrolimus (therapeutic range 5–8) and Mycophenolate (2 gram daily). Prednisolone was started with a dose of 20 milligram (mg) and then gradually reduced to 5 mg over a period of 3 months. All recipients of kidney transplant from a heart beating deceased donor or live donor also received Basiliximab 20 mg before implantation and 4th post operative day. However transplant recipients from non heart beating donors received Daclizumab instead. The transplants carried out before 2006 received a Cyclosporine and Azathioprine based immunosuppression regimen. The intra-operative diuretics regimen used was variable according to surgeon's choice. One surgeon used no diuretics in any of his patients (GND), one surgeon used Furosemide 80 mg and another surgeon 250 mg and one used Mannitol 20 g in GD before revascularization of the kidney. The recipients were kept well hydrated during and after the transplants especially in immediate post operative period. All recipients were given intravenous fluids to maintain a central venous pressure (CVP) between 10 and 12 mm Hg (millimeter of Mercury) and when a stable CVP was achieved, intravenous fluid equal to 50 mL plus previous hour urine output was given. The most common intravenous fluid used was a combination of normal saline and 5% dextrose water. A baseline biopsy was part of transplant protocol in all cases, followed by a biopsy on day 7 only in the cases of delayed graft function. An ultrasound scan on day 1 was also part of protocol to ensure satisfactory perfusion and to exclude hydronephrosis.

The hospital database system and case notes were used to obtain the patient demographics and other relevant data. The basic demographics included age, gender, HLA mismatch status, cold ischemia time, warm ischemia time and pre-operative renal function of the donor. Outcome measures were incidence of delayed graft function and a comparison of graft and patient survival in both groups. SPSS 15.0 was used for statistical analysis and Kaplan–Meier curve to measure graft and patient survival. Mann–Whitney *U* test was used to compare medians and student t- test to compare means between different groups. A *p* value of less than 0.05 was considered as significant.

3. Results

3.1. The survey

Forty surgeons answered the questionnaire from 18 transplant centres with a response rate of 67%. 13 surgeons did not use any intra-operative diuretics for renal transplantation. Mannitol was used by 10/40, Furosemode 6/40 and 11 surgeons used a combination of both including one using Dopamine in addition. The dose range of Furosemide was 20–250 mg and Mannitol 1G to 20 g per kg body weight. One surgeon excluded diuretics for living donor transplants and another gave Furosemide 40 mg as compared to a combination of Mannitol and Furosemide for deceased donors transplants. Out of 18 centres, only in 7 centres all surgeons had a consistent policy of using same diuretic regimen.

3.2. The comparison of GD versus GND

The GD consisted of 45/69 deceased donor and 24/69 living donor transplants as compared to 58/80 deceased donors and 17/80 living donors in GND. The donor and recipient characteristics in both groups were comparable as given in Table 1. There was no significant overall difference in one year graft survival of GD versus GND ($N = 65/69$, 94% and 75/80, 94% respectively, $p = 0.08$) and the incidence of delayed graft function was also comparable (16/69, 23% and 21/80, 26% respectively, $p = 0.07$). The incidence of delayed graft function showed a better trend in living donor transplants in GND but rest of the outcome measures were comparable as given in Table 2. The patients with DGF under went renal transplant biopsy which revealed acute rejection in 11, acute tubular necrosis 9 and CNI toxicity in 1 patient in GND. Whereas the biopsies in GD with DGF revealed acute rejection in 4 and ATN in 9 recipients of cadaveric donor grafts and 2 acute rejections and 1 indeterminate biopsy in living donor transplants (Table 2). Kaplan–Meier survival curve measured 5 year patient survival 94% (Confidence Interval 95%, 93-96) in GND and there was no patient loss in 12 months follow-up of GD.

4. Discussion

It has been well established that adequate hydration and stable blood pressure have beneficial effect on the transplanted kidney and the incidence of DGF and ATN can be reduced by these measures.[14] However there is very little data which could firmly support that any clinical benefit could be achieved by the use of diuretics such as Furosemide or Mannitol intra-operatively. That is probably the reason for a significant variation in clinical practice of use of intra-operative diuretics by different surgeons as shown by the survey presented in this study. Out of 18 centres, only in 7 centres all surgeons had a consistent policy of using same diuretic regimen. The dose of diuretics was variable from centre to centre and there was a variation in practice on the choice and dose of diuretics by the same surgeons for different patients depending upon the donor type. Moreover 13 out of 40 surgeons did not use any diuretics. This clearly showed a lack of any consistent and replicable policy and the choice of diuretics or no diuretics is purely dependent on surgeon's preference and is not based on any robust clinical evidence. It would be important to mention that Tiggler et al. in a study published in 1985 showed that there was some added benefit in reducing ATN after combining moderate hydration

Table 1
A comparison of donor and recipient characteristics in diuretics and no-diuretics groups.

Donor and recipient characteristics	Group Diuretics	Group No-Diuretics
Recipient age (Years)	40 ± 14	42 ± 16^^
Donor age (Years)	42 ± 16	43 ± 16^^
Donor retrieval creatinine (umol/L)	81 ± 33	86 ± 31^^^
Cold ischemia (hours)		
Cadaveric donor	17 ± 3	17 + 5^
Living donor	2½ ± 1	2 ± 1^^
Warm ischemia (Minutes)		
Cadaveric donor	30 ± 7	33 ± 7^^
Living donor	31 ± 9	31 ± 6^
HLA mismatch	2 (1–4)	2 (1–4)^
Median and IQR		

umol/L micromole per litre, HLA human leukocyte antigen, IQR interquartile range, *P* value 0.08^, 0.07^^, 0.06^^^ Mann–Whitney *U* Test and student *t* test.

Table 2
Graft survival in Group Diuretics (GD) and No-Diuretics (GND) and associated ATN.

	Group Diuretics N, (%)	Group No-diuretics N, (%)
Deceased donors	$N = 45$	$N = 63$
One year graft survival	42, (93)	58, (92)^
Delayed graft function	13, (29)	21 (33)^^
Five year graft survival	NA	58 (92)
Living donors	$N = 24$	$N = 17$
One year graft survival	23, (96)	17 (100)^^
Delayed graft function	3, (13)	0^^^
Five year graft survival	NA	17 (100)
All transplants[a]	$N = 69$	$N = 80$
One year graft survival	65, (94)	75 (94)^
Delayed graft function	16, (23)	21 (26)^^
ATN	9 (13%)	9 (11%)^^^

[a] All transplants deceased and living donors, NA not applicable (12 months follow up only for GD), N Number, ATN acute tubular necrosis on transplant biopsy, p value 0.08^, 0.07^^, 0.06^^^, Kaplan–Meier curve and student t test.

with Mannitol before revascularisation as opposed to restricted fluid regimens with or without Mannitol.[13] However it was not clarified if moderate hydration alone would give similar ATN rate or not when compared to moderate hydration and Mannitol regimen. Our study has clearly shown that diuretics use not only varies from centre to centre but also from surgeon to surgeon. Similarly in current literature there is no consensus as to the practice of intra-operative fluid replacement (crystalloid or colloid), how much they should be given, use of Mannitol, Furosemide and Dopamine. The practice varies from centre to centre, individual surgeons within the same centre and even anaesthetists within the same centre.[14–17] All patients in our study received moderate hydration with a uniform fluid replacement protocol to keep CVP 10–12 mm Hg. The goal is to keep CVP above 10 mm Hg so that the intravascular compartment, which often is contracted prior to renal transplant, is filled up particularly just before the release of clamps. This is done in order to minimize the chances of ATN. The earlier the occurrence of this episode the greater will be the likelihood of graft dysfunction.[9,12–14]

The donor risk factors in both GD and GND were comparable (Table 1). The incidence of DGF was numerically better in GD (29%) as compared to GND (33%) in case of deceased donor transplants and inferior (GD 13% versus GND 0) in case of living donor transplants. Nevertheless there was no significant difference noted in DGF, ATN and one year graft survival in each group (Table 2). All living donor recipients ($n = 17$) in GND had a functioning graft at 5 year follow-up. This finding was limited by the fact that we had not as yet reached to a stage of 5 year follow-up figure for GND but no difference in one year graft survival was noted in either group (94%). The study findings show no significant difference in terms of reduction in ATN or DGF and improvement in graft survival with or without the use of diuretics as long as patients are moderately hydrated.

Transplant recipients vary widely in terms of their respective pathological state. They might have Type II Diabetes, advanced cardiomyopathy, vasculitis, sickle cell disease and morbid obesity. Hence intra-operative fluid management and diuretic use should be case specific. To stress upon the above mentioned observation one must consider that there is a significantly high incidence of myocardial dysfunction in patients with renal failure and particularly those on dialysis.[18] Observational studies indicate that congestive heart failure (CHF) is 12–36 times more prevalent in dialysis patients as compared with the general population.[19–21] It has been demonstrated by Wali et al that kidney transplantation can be performed safely in ESRD (end stage renal failure) patients with decreased LVEF (left ventricular ejection fraction) (<40%), advanced heart failure, and without inducible ischemia. Kidney transplantation resulted in an increase in LVEF in more than 86% of patients. Even a majority of patients with pre-transplant LVEF <20% had normalized LVEF in the post-transplant period.[18] It is important to emphasize that in these high risk patients, intra-operative fluids/diuretics are given cautiously and the whole practice is tailored according to the patient's cardiovascular status. This can be measured and calibrated during surgery not only by CVP but also by non invasive methods of cardiac output monitoring. The practice of giving diuretics or no diuretics, the volume and the kind of fluid (crystalloid or colloid or both), Dopamine infusion and its dose depends on specific indicators of a particular patient.

It is a small size study but at least the findings highlight the need for a well designed randomized controlled trial to clarify the rationale of use of intra-operative diuretics in renal transplantation. The unnecessary use of diuretics can have potential detrimental effects on the renal transplant recipient and their use may have some cost implications but there is no firm evidence to support this and vice versa and that is why more studies are required for the assessment of clinical risks versus benefits.[22,23]

5. Conclusion

The study has shown that there is a huge variation in clinical practice of the use of intra-operative diuretics in renal transplantation in the United Kingdom. The role of diuretics in reducing the incidence of acute tubular necrosis and delayed graft function is equivocal. Moreover the study did not show any relation between the use of diuretics and improvement in renal graft survival. Each patient needs an individualized intra and post operative regimen according to the end stage kidney disease and the comorbidities. The results of the study emphasize the need for well designed larger studies to clarify the role of the use of intra-operative diuretics during renal transplant surgery.

Ethical approval

Ethical approval was not required. This is a survey and retrospective analysis of case notes and did not require formal ethics approval according to current guidelines. It falls under the category of "Service Evaluation".

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None.

Conflict of interest

There are no conflicts of interest related to this study.

Author contributions

Faisal Hanif and Enric Murio designed the study and all authors contributed in data collection, literature review and manuscript writing.

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