

The Effect of Non-Invasive Goal Directed Fluid Administration on Graft Function in Deceased Donor Renal Transplantation: A Pilot Study

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Received 31 March 2016; accepted 28 August 2016; published 31 August 2016

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Abstract

Background: Non-invasive goal directed fluid therapy during deceased donor renal transplant (CRT) may reduce the incidence of delayed graft function. Plethysmograph Variability Index (PVI) has been shown to predict fluid responsiveness during surgery. This pilot study evaluated the feasibility of goal directed fluid administration protocol based upon PVI studying the incidence of delayed graft function (DGF) in renal transplant recipients. **Methods:** Twenty patients underwent primary CRT. The Control group received intravenous fluid (IVF) at a calculated constant rate. The Treatment group received a baseline IVF infusion throughout the surgery. PVI values greater than 13% were treated with 250 ml boluses of IVF. Primary end point was DGF; total IVF administration and urinary biomarker NGAL levels were secondary endpoints. **Results:** Treatment group at every time point received significantly less IVF. There was no significant difference in incidence of DGF between the groups. 2 patients in the Control group and 6 in the Treatment group developed DGF. NGAL was not associated with the group assignment or total IVF given ($p < 0.2$). **Conclusions:** The effectiveness of goal directed fluid therapy with non-invasive dynamic parameters has not been validated in renal transplant surgery and larger prospective studies are needed to determine its utility in renal transplantation.

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How to cite this paper: Whiteley, J.R., Taylor, J.M., Freely Jr., J.J., Epperson, T.I., Bell, L., Murray IV, J.L., Bratton, C.F. and Hand, W.R. (2016) The Effect of Non-Invasive Goal Directed Fluid Administration on Graft Function in Deceased Donor Renal Transplantation: A Pilot Study. *Open Journal of Organ Transplant Surgery*, 6, 13-21.
<http://dx.doi.org/10.4236/ojots.2016.63003>

Keywords

Deceased Donor Renal Transplant, Non-Invasive Goal Directed Fluid Therapy, Delayed Graft Function, Plethysmograph Variability Index

1. Introduction

Delayed graft function (DGF), a form of acute kidney injury occurring immediately after renal transplantation, affects 2% - 50% of deceased donor kidney transplant recipients [1]. The incidence varies widely in part due to inconsistent diagnostic criteria: no less than 7 functional definitions exist [2]. The need for dialysis within seven days of transplant is the most common definition and thus, the definition used in this manuscript [3]. Morbidity and mortality are increased with DGF and it is a risk factor for the development of acute rejection while also decreasing long-term graft survival [4]. Limiting the ischemia-reperfusion injury believed to cause DGF and also to identify patients at increased risk for the development of DGF continues to be the focus of research [3] [5]-[7]. Detection of urine biomarkers including neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule have been identified within 24 hours of transplant [8]-[12].

Despite advancements in surgical technique and immunosuppression, the number of transplant recipients affected by DGF remains unacceptably high. Many of the known risk factors are non-modifiable and related to expansion of the organ donor pool (extended criteria donors). Known risk factors for DGF include: donor age greater than 55, need for vasopressor support before organ procurement, donor death by stroke, donor diabetes and hypertensive disease and recipient age [13]-[16]. Another significant risk factor for DGF is the (cold) ischemic time (CIT); this is only partially modifiable given the logistics of transplantation.

It is unclear whether intraoperative hemodynamic management of recipients affects DGF. Traditionally, intraoperative care has consisted of generous (empiric, weight based) administration of intravenous fluid (IVF) during the pre-anastomotic phase of kidney transplant, based on early work by Carlier *et al.* [17]. This work showed earlier graft function and decreased incidence of acute kidney injury in recipients with higher CVP and PA pressures. More recent work by Othman *et al.* demonstrated CVP-guided crystalloid administration results in increased immediate urine production and decreased time required for urine production [18]. Unfortunately, the pilot data did not make any statements regarding the effect of directed fluid administration on DGF, a more meaningful outcome.

Hemodynamic optimization with fluid and vasoactive drugs has been shown to improve outcomes in high-risk surgical patients [19]. This enhancement has been facilitated with protocols directed by data from devices such as pulmonary artery catheter, arterial line or esophageal doppler. Stroke Volume maximization guided by esophageal Doppler has been shown to reduce complications [20], decrease hospital stay [21] and reduce the incidence of critical care admission [22]. Studies have shown that variation in the arterial pressure waveform during mechanical ventilation is a reliable indicator of fluid responsiveness [23]-[25]. Michard *et al.* demonstrated that pulse pressure variation is an accurate predictor of fluid responsiveness and dramatically better than cardiac filling pressures [23]. The monitoring technologies used in the goal directed fluid administration studies are rapidly developing and the ability of non-invasive monitors to predict fluid responsiveness have recently been published. Many hemodynamic monitors calculate dynamic parameters like the plethysmograph variability index (PVI) which is derived from a non-invasive pulse oximeter. PVI is the percentage variation in the plethysmograph and is calculated from the perfusion index (PI), which is described as the percentage of light absorbed as a result of arterial pulsation (AC) relative to total amount of light absorbed (DC).

$$PI = (AC/DC) \times 100\%.$$

The PI represents the ratio of non-pulsatile to pulsatile blood flow through the peripheral capillary bed. The PVI is then derived from changes in PI throughout the respiratory cycle of ventilated patients.

$$PVI = \left\{ \left(\frac{PI_{\max} - PI_{\min}}{PI_{\max}} \right) \times 100\% \right\}.$$

Because changes in the amplitude of the pulse oximeter plethysmograph correlate closely with variation in pulse pressure [26] [27]; the plethysmographic variability is able to predict fluid responsiveness in surgical pa-

tients [28] [29]. PVI values greater than 13% have been shown to predict fluid responsiveness in surgical patients [30] [31].

Given the importance of DGF on long term recipient morbidity and mortality and the possible benefits of goal-directed fluid administration, the authors hypothesized that a goal-directed fluid administration protocol based on PVI might decrease the incidence of DGF in primary, deceased donor kidney transplant recipients. Due to the logistics of transplantation, competitive pharmaceutical trials, limited baseline information with which to perform a power analysis, and the paucity of data demonstrating safety of fluid “restriction”, the study was designed as a prospective, randomized pilot investigation to aid future work.

2. Methods

IRB approval and written informed consent were obtained from 20 patients undergoing deceased donor kidney transplantation at the Medical University of South Carolina (Charleston, SC) between January and November 2013. Extended criteria donors (ECD) were included in the donor pool. All adult dialysis-dependent patients undergoing primary (single organ) deceased donor renal transplant were considered for enrollment. Surgeries were all performed by one of six-fellowship trained abdominal transplant surgeons. Surgical technique was standardized within the institution involving a curvilinear incision in a lower quadrant of the abdomen, with division of the muscles of the abdominal wall and dissection of the retroperitoneal space to expose the iliac vessels and the bladder. This approach involves end-to-side anastomosis of the renal artery to the external iliac artery; if unacceptable, the common iliac used. Exclusion criteria were: previous organ transplant, severe anemia (Hgb < 7), known cardiomyopathy or valvular disease, left ventricular dysfunction with LVEF < 50%, symptomatic coronary artery disease, or enrollment in other DGF related trial(s). Patients were randomized to the control or study group at the time of enrollment by random number generator. Our team of five transplant surgeons performed all surgeries. There was no blinding of any practitioner.

2.1. Anesthetic Management

All patients received Midazolam as an anxiolytic as needed prior to leaving the holding area. Choice of intravenous induction agents was at the discretion of the attending anesthesiologist and could consist of any combination of the following: Fentanyl, Hydromorphone or Morphine; Lidocaine; Diprivan or Etomidate; and Succinylcholine, Cisatracurium, Rocuronium or Vecuronium. Anesthesia was maintained with either Sevoflurane or Isoflurane (0.70 - 1.1 MAC) alone with opiate analgesia as needed. All recipients received 4 mg Ondansetron thirty minutes prior to emergence. All recipients received reversal of neuromuscular blockade with standard doses of Neostigmine and Glycopyrrolate. Induction immunosuppression regimen utilized in renal transplantation during the study period included anti-thymocyte globulin (Thymoglobulin; Genzyme, Cambridge, MA) or IL2-R antagonist (Basiliximab (Simulect; Novartis, Basel, Switzerland). Lower immunologic risk recipients (PRA < 80%, non-retransplant, CIT < 24 hrs) received IL2-R antagonists and high-risk patients received anti-thymocyte globulin. All patients received methylprednisolone at the time of renal transplantation. These medications are standard of care for patients undergoing this procedure at the institution and obtained from a centralized hospital pharmacy without any blinding or study-related-controls.

2.2. Monitoring

All patients had basic ASA monitoring and arterial catheters were placed based on patient specific comorbidities, as they are not standard at our hospital. In addition a Masimo Radical 7 monitor using M-LNCS adult plethysmograph (Masimo Corp, Irvine CA) was attached to a finger in all patients. This is a non-invasive and disposable fingertip adhesive monitor. Data from all monitors was recorded electronically in our electronic medical record and within devices themselves. No plethysmographs were placed on extremities with blood pressure cuffs.

2.3. Goal Directed Fluid Management

All intravenous fluid (IVF) used was either Lactated Ringers or Plasmalyte and was administered via a programmable infusion pump. All patients received one liter of IVF over the first 30 minutes following intubation. Patients in the Control group received IVF at a rate determined by the following equation: $(70 \text{ ml/kg} \times \text{patient weight in kilograms})/160 \text{ min}$. This rate was derived from our local historical total fluid administration standards

and average surgery time of 160 minutes.

Patients in the Treatment group received IVF at a rate of 5 ml/kg/hr throughout the case as a background infusion. Additional fluid was bloused based on the PVI beginning at the moment the graft kidney was removed from ice (warm ischemia). Fluid boluses (250cc) were given until PVI < 13% through the end of positive pressure ventilation (emergence).

2.4. Hemodynamics

In addition to fluid administration as described above, systemic blood pressure was maintained within 20% of the pre-anesthetic baseline in both groups. To achieve this goal, the anesthesia providers were permitted to titrate the volatile anesthetic (0.7 - 1.1 MAC) and/or initiate vasopressors. (Dopamine up to 10 mcg/kg/min followed by Phenylephrine up to 40 mcg/kg/min). If the hemodynamic goal was not met with these measures in the Control group, providers were instructed to administer additional IVF as needed not to exceed 70 ml/kg/case. If the hemodynamic goal was not met in the Treatment group, providers were instructed to give additional IVF as needed and these recipients would be withdrawn from the study protocol. Anesthesia providers were instructed to make every effort to wean or discontinue vasopressors if the blood pressure allowed.

2.5. Postoperative Care

All patients recovered in the same post anesthesia care unit and post-surgical hospital floor. All care after emergence was standardized without regard (or even knowledge) of Treatment/Control study status. Post-operative maintenance immunosuppression therapy consisted of an antiproliferative agent (Mycophenolate Mofetil (MPA) (CellCept; Roche, Nutley, NJ), a calcineurin inhibitor (Tacrolimus (Prograf; Astellas, Tokyo, Japan) and low-dose corticosteroids. Programmatic immunosuppression dosing guidelines included: MPA 2000 mg/day, FK 0.1 to 0.15 mg/kg/day divided doses (8 - 12 ng/ml \leq 3 mo, 7 - 10 ng/ml 3 - 12 mo, 7 - 7 ng/ml after 12 mo). All patients were followed with standard programmatic interval laboratory assays including white blood cell count (WBC (cells/ μ L)), serum creatinine (mg/dL), FK (ng/ml). Fluid balance was achieved via matching ins and outs for the first 48 hours with IVF (0.45% Normal Saline). Patient progress toward discharge was based on standard landmarks (pain control, ambulation, kidney function, and bowel function).

2.6. Outcomes

All patients were followed for the duration of their inpatient stay with serial labs. Serum creatinine was recorded at 12 hours and then daily with standard serial labs. Nursing documentation was used for daily fluid balance values. Need for dialysis was at the discretion of the transplant nephrology team and binary outcome based on dialysis on or before postoperative day 7. Morbidity and mortality outcomes were retrieved from records after discharge. A single urine sample was obtained at 24 hours after reperfusion. This sample was processed and stored frozen until batch processing at the O'Brien Center for AKI Research (University of California San Diego), where NGAL assay was performed (7-plex, Meso Scale Diagnostics, Rockville, MD).

3. Statistical Analyses

The primary outcome of interest was whether or not a patient experienced delayed graft function (DGF). Univariate associations between DGF and categorical variables were evaluated using Fisher's exact test where appropriate. Associations between DGF and all continuous variables were evaluated using the Mann-Whitney U test. Due to small sample size, no multivariate modeling was considered, where appropriate p-value of 0.05 was considered statistically significant.

As a secondary analysis we examined the association between the biomarker NGAL levels and total amount of IVF given, Treatment group designation, and occurrence of DGF. NGAL values were log transformed to improve normality. Associations between the biomarkers and total IV fluid were examined using Pearson's correlation. Associations between NGAL levels and treatment group or with occurrence of DGF were examined using t-tests or Wilcoxon rank sum test where appropriate. All analyses were conducted in SAS v.9.3 (Cary, NC)

4. Results

The mean age of study participants was 52.9 + 9.1 years. A majority of the participants were male and non-

white (60% and 75% respectively). Characteristics of the study population by Treatment group are shown in **Tables 1-3**. There was not a significant difference between the Control and Treatment group in age, gender, race, weight, height, BMI, time since last dialysis, PRA matching score, and cold or warm ischemic time. Max PVI,

Table 1. Treatment and control demographics.

Variable	Control (n = 10)	Treatment (n = 10)	p
Age	54.1 (10.5)	51.7 (7.83)	0.658
Weight	94.5 (19.0)	108.4 (23.3)	0.141
Height	174.4 (11.1)	170.0 (32.3)	0.94
BMI	30.9 (4.46)	33.6 (2.43)	0.064
Gender (Male)	70.0 (7)	50.0 (5)	0.65
ASA 4	40.0 (4)	30.0 (3)	1
Time since last dialysis	35.8 (33.1)	39.2 (16.5)	0.327
PRA score	23.4 (35.9)	29.2 (34.5)	0.458
Race (white)	30.0 (3)	20.0 (2)	1

Table 2. Treatment and control donor information.

Variable	Control (n = 10)	Treatment (n = 10)	p
Donor age	27.4 (13.0)	46.1 (7.03)	<0.001
Donor hypertension (yes)	20.0 (2)	40.0 (4)	0.629
Donor DM (yes)	0.00 (0)	20.0 (2)	0.474
Donor on pressors (yes)	70.0 (7)	77.8 (7)	1
Extended criteria donors (yes)	0.00 (0)	20.0 (2)	0.474

Table 3. Treatment and control intraoperative characteristics.

Variable	Control (n = 10)	Treatment (n = 10)	p
Duration OOI	47.3 (14.9)	59.6 (19.3)	0.173
IVF OOI	2740 (757.5)	1331 (423.9)	0.001
IVF anastomosis	3547 (765.2)	1749 (792.0)	<0.001
IVF total	4685 (773.9)	2851 (1058)	<0.001
Anastomosis time	54,336 (14222)	59238 (18425)	0.473
Cold ischemic time	1167 (405.3)	1051 (426.6)	0.705
Warm ischemic time	34.5 (5.06)	38.4 (5.40)	0.149
KDPI score	31.9 (24.7)	55.5 (8.76)	0.023
Duration of surgery	150.5 (20.1)	263.3 (218.6)	0.005
Estimate blood loss	212.0 (115.5)	295.0 (177.1)	0.252
UOP intraoperative	1249 (1874)	297.2 (290.1)	0.241
Max PVI	24.3 (10.2)	19.8 (5.47)	0.395
Kidney on pump (yes)	70.0 (7)	80.0 (8)	1
OOI vasopressor use	20.0 (2)	10.0 (1)	1
Anastomosis vasopressor (yes)	20.0 (2)	10.0 (1)	1
Vasopressor at anastomosis	10.0 (1)	10.0 (1)	1
Vasopressor at surgery end (yes)	40.0 (4)	10.0 (1)	0.303
DGF	20.0 (2)	60.0 (6)	0.17
NGAL	13.1 (0.47)	13.9 (0.42)	0.273

estimated blood loss, intraoperative urine output, presence of donor hypertension and diabetes mellitus, ECD, donor vasopressor use, vasopressor use at time of anastomosis or the end of surgery did not have a significant difference between the two groups. There was no significant difference between the two groups and incidence of DGF. Specifically, 2 patients in the Control group developed DGF compared to 6 in the Treatment group ($p = 0.17$).

Patients in the Treatment group received significantly less IVF at every time point (start of surgery to initiation of warm ischemic time, warm ischemia period, and anastomosis to surgery end) ($p \leq 0.001$). There were significant differences between the donor ages with patients in the Treatment group having significantly older donors relative to the control group ($p < 0.001$). There was also a significant difference in the Kidney Donor Profile Index (KDPI) [32] scores between the Control and Treatment group. The Treatment group had significantly higher KDPI scores ($p = 0.023$). Duration of surgery was also significantly longer in the patients that received goal directed fluid therapy ($p = 0.005$).

Occurrence of DGF was not associated ($p = 0.5$) with the urine NGAL (creatinine adjusted). Similarly, NGAL was not found to be associated with being assigned to the Treatment group or total IVF given ($p > 0.2$). **Table 3** reflects these results.

5. Discussion

DGF confers significant risks for patient morbidity and mortality as well as increased health care cost. Over aggressive or targeted IVF intraoperative fluid administration often exacerbates post-operative risk profile. This pilot study set out to evaluate the feasibility of a goal directed fluid administration protocol based on PVI with the goal of decreasing the incidence of DGF in primary deceased donor kidney transplant recipients. We believe the methodology of this pilot serve as a meaningful confirmation that such a study can be performed. We present the pilot results from our small sample. While not reaching statistical significance, DGF was more common in the Treatment group than Control (6 vs. 2 patients). The Treatment group had significantly higher donor age and KDPI. Elevated donor age and KDPI are known independent risk factors for DGF after renal transplantation. The urine proteomic marker NGAL showed no correlation with outcomes, and thus its predictive utility was not confirmed in our small sample. We believe it is important to publish these “negative” finding in hopes of providing impetus and direction for further research. We will describe our findings and possible limitations of this research.

The intervention did not reduce the incidence of DGF, and there are at least three plausible reasons the hemodynamic protocol was ineffective. First, the treatment algorithm employed may simply not be optimal to this patient population. In our study, IVF was administered intra-operatively to attain a PVI below 13%. As mentioned earlier, the amount and timing of IVF administration may be equally fundamental to intraoperative fluid management [33]. The limitation of IVF administration before the initiation of the warm ischemic period was chosen based on the principle that approximately 80% of an IVF bolus extravasates within 30 minutes [34] [35]. The authors believed the accumulation of non-circulating volume might prove injurious or, at best, not be beneficial in terms of post-transplant renal function. In colorectal surgery, for example, there is increasing evidence that optimization of the circulating volume early in surgery is important in decreasing the inflammatory response and improving outcomes [36]. Perhaps a different protocol (e.g. timing, trigger, volumes) might demonstrate benefit as we still believe there may be harm caused by such large volumes of (unguided) fluid administration.

Second, our regimen of IVF administration for PVI greater than 13% may not have optimized volume status enough during the warm ischemic time. Plethysmographic variability has been shown to predict fluid responsiveness in cardiac [30], general surgical [37] and intensive care patients [28], and goal directed fluid administration protocols directed by PVI have been shown effective at reducing morbidity and length of stay [27] [30] [38]. For dialysis-dependent patients, it is possible that the plethysmographic signal being used to calculate PVI may not be usable. These patients have serial interventions involving arterial vessels proximal to the site used for sensor placement (*i.e.* temporary dialysis catheters, arteriovenous shunts). Given the subtle changes calculated within PVI, any aberration in arterial tone or integrity may have invalidated PVI. Given the potential importance of appropriate fluid administration, it may be most appropriate to repeat this study using a more central (esophageal doppler) monitoring to direct fluid management.

Finally, a potential confounding variable to our study is the unique pathophysiology that dialysis may cause a patient presenting for kidney transplantation. Anesthesiologists administer IVF based on several physiologic

principles that may not remain intact due to the side effects of hemodialysis [39]. Hemodialysis patients must develop an ability to function despite large fluctuation of total body water (often have more than a kilogram of weight removed per dialysis session to achieve “dry weight”). Their heart, lungs, and vasculature has adapted to tolerate (functionally prefer?) hypervolemia. Therefore, it is possible that standard models to direct fluid administration may simply not apply, and, despite being anecdotal, the historical precedent of high-volume IVF administration may actually optimize renal outcomes.

This report is limited by confounding variables as any such pilot project related to deceased donor renal transplantation attempting to demonstrate an improvement on DGF. While we have shown no difference in cold or warm ischemic time, there was no prospective matching or controlling these important factors. Similarly, the donor age and KDPI values were higher within the Treatment group, which may have contributed to the (statistically insignificant) increased incidence of DGF. Finally, the surgical times were longer for patients in the treatment wing, and while this research was not designed to evaluate the potential role of IVF administration on surgical duration or complication, it is plausible that a relationship does exist. Any surgical difficulty (perhaps with vascular anastomosis) caused by the PVI directed fluid administration certainly may have increased the incidence of DGF.

6. Conclusion

Dynamic predictors of fluid responsiveness have been shown to be useful in identifying patients who will respond to a fluid challenge with a concomitant increase in cardiac output. Clinical use of guided fluid therapy has increased significantly in the last fifteen years [35]. Studies have yielded conflicting results, but using goal directed fluid therapy has been shown to decrease post-surgical morbidity and ICU length of stay [40]. The effectiveness of goal directed fluid therapy with non-invasive dynamic parameters has not been validated in renal transplant surgery. Larger, novel, prospective studies with long term follow-up should be conducted to determine if there is a benefit in goal directed fluid therapy for patients undergoing deceased donor renal transplantation.

Conflicts

All authors have reported no conflicts of interest.

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