Plasma electrolyte imbalance in pediatric kidney transplant recipients

Running title: Post transplant electrolyte imbalance

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Keywords

Kidney transplantation, Water-Electrolyte Imbalance, Sodium Chloride, Children, Brain Edema

Abstract

Background

In current practice, pediatric kidney transplant recipients receive large volumes of intravenous fluid intraoperatively to establish allograft perfusion, and further fluid to replace urinary and insensible losses postoperatively. Acute electrolyte imbalance can result, with potential for neurological sequelae.

We aimed to determine the incidence and severity of postoperative plasma electrolyte imbalance in pediatric kidney transplant recipients managed with the current standard intravenous crystalloid regimen.

Methods

A retrospective analysis of plasma electrolytes in the first 72 hours post kidney transplant in 76 children transplanted between 1 January 2015 and 31 January 2018, managed with a standard intravenous fluid strategy used in most UK pediatric transplant centres.

Results

Of 76 pediatric transplant recipients of median age 9.9 (range 2.2 – 17.9) years predominantly managed with 0.45% sodium chloride 5% glucose, 45 (59%) developed acute hyponatremia, 23 (30%) hyperkalemia and 43 (57%) non-anion-gap acidosis in the postoperative period. Hyperglycemia occurred in 74 (97%) patients. Hyperkalemia was more prevalent in deceased than live donor recipients ($p = 0.003$), and was significantly associated with non-anion-gap acidosis ($p<0.001$). Recipient weight was not associated with overt electrolyte imbalance.

Conclusion

Postoperative plasma electrolyte imbalance is common in pediatric kidney transplant recipients. Current clinical care strategies mitigate the associated risks of neurological sequelae to some degree.

Further studies to optimise intravenous fluid therapy and minimise electrolyte disturbance in this group of patients are needed.

Introduction

Pediatric kidney transplant recipients receive large volumes of intravenous fluid in order to establish and maintain allograft perfusion.[1] In addition to intraoperative crystalloid volumes approaching 200ml/kg bodyweight, large volumes can be administered postoperatively to replace urine losses related to acute tubular injury. Acute electrolyte imbalance can result, which can lead to seizures, cerebral oedema and death.[2,3] The risks associated with acute changes in plasma electrolyte concentrations and osmolality are mitigated by frequent monitoring, initially 2 to 4 hourly in routine pediatric kidney transplant care.

The majority of UK pediatric kidney transplant centres use 0.45% sodium chloride 5% glucose postoperatively. This is largely due to concerns about hyperchloremic metabolic acidosis with 0.9% sodium chloride, and hyperkalaemia with potassium containing balanced fluids. Two of 10 UK pediatric transplant centres recently changed to 0.9% sodium chloride to replace urine losses due to the risk of hyponatremia with hypotonic solutions (personal communication).

We undertook a single centre retrospective analysis of 76 pediatric kidney transplant recipients managed with 0.45% sodium chloride 5% glucose in order to determine the incidence and severity of acute postoperative plasma electrolyte imbalance.

Patients and Methods

Pseudo anonymized data were collated from all children under 18 years of age who underwent kidney transplantation at our institution between 1 January 2015 and 31 January 2018. Data included all plasma electrolyte results for the first 72 hours after returning from the operating room, anthropometric data, donor type, allograft placement and fluid administered. Ethical approval was given for extraction and analysis of the pseudo anonymized data, with patient and family consent waived due to the anonymised retrospective design.

Clinical laboratory reference ranges for plasma electrolyte concentrations were used to assess abnormalities. Hyponatremia was defined as plasma sodium concentration < 135mmol/l, hyperkalemia as plasma potassium concentration > 5.5 mmol/l, hyperglycemia as blood glucose > 5.5mmol/l and non-anion gap acidosis as plasma bicarbonate < 20mmol/l with anion gap < 20mmol/l. Estimated GFR was calculated using the updated creatinine based Schwartz formula. [4] The rate of change of eGFR was determined from eGFR calculated postoperatively and at 72 hours post-transplant.

Electrolyte abnormalities were compared between patients in various groups, including patient weight and donor type (living vs deceased). A threshold of 20kg was used for weight because most children under 20kg have intra-abdominal as opposed to extra-peritoneal graft placement.

Continuous data are reported as median (range), and proportions as number (%). Continuous variables were compared using the Wilcoxon rank sum test with continuity correction. Categorical variables were compared using Fisher's exact test. All analyses were performed using R (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/)

Results

All seventy six pediatric transplant recipients of median age 9.9 (range 2.2 – 17.9 years) transplanted at our institution between 1 January 2015 and 31 January 2018 were included. Baseline characteristics of the cohort are outlined in table 1. Forty nine (64%) had living related donors, and 18(24%) weighed less than 20kg. Seventeen (94%) smaller recipients weighing under 20kg had intra-abdominal anastomoses onto the aorta and inferior vena cava, with one extraperitoneal placement in this group. The proportion of live donor transplants was similar in smaller and larger recipients; 13 (72%) of 18 smaller recipients and 36 (63%) of 58 larger recipients had live donors (p = 0.6).

All patients were initially managed with 0.45% sodium chloride with 5% glucose to replace insensible losses and urine output postoperatively. Intraoperative crystalloid comprised either Hartmann's solution or 0.9% sodium chloride.

In the first 72 hours post-transplant, hyponatremia developed in 45 (59%) of 76 children, hyperkalemia in 23 (30%) and non-anion-gap acidosis in 43 (57%) (figure 1). Hyperkalemia was significantly associated with non-anion-gap acidosis ($p<0.001$). Hypernatremia was evident in 20 (26%) and hypokalaemia in 14 (18%) patients. Seventy four (97%) children experienced hyperglycemia (table 2).

One patient with hyponatremia experienced seizures in the post-transplant period. There were no seizures in patients who did not experience hyponatremia.

Neither the volume of fluid received, nor the proportional weight gain, differed significantly in patients who developed hyponatremia compared to those who did not develop hyponatremia (table 2).

Deceased donor recipients had significantly lower bicarbonate and higher potassium levels than living donor recipients ($p < 0.0001$, $p = 0.0006$ respectively, Figure 2). Overt hyperkalemia (>5.5mmol/l) was more prevalent in deceased donor recipients ($p = 0.003$, table 3). Donor type did not affect the incidence of hyponatremia or acidosis (p = NS, table 3). The postoperative rate of improvement in eGFR was significantly lower in deceased donor recipients ($p = 0.001$, figure 4A).

Transplant recipients weighing less than 20kg had higher sodium ($p < 0.0001$), lower potassium ($p<0.0001$), higher chloride ($p<0.0001$) and lower bicarbonate($p = 0.02$) than larger children (figure 3). Despite these trends, recipient size did not significantly affect the incidence of overt electrolyte abnormalities outside laboratory reference ranges (p = NS, table 3). The rate of change of eGFR did not differ significantly by patient size (figure 4B).

Discussion

These data confirm that postoperative electrolyte imbalance is common in pediatric kidney transplant recipients, in particular hyponatremia and non-anion gap acidosis. Overt hyperkalemia was more evident following deceased donation; donor size was not associated with clinically significant electrolyte abnormalities.

Development of acute hyponatremia is a particular concern in pediatric kidney transplant recipients, as it is associated with neurological sequelae including seizures[3], cerebral edema and death in extreme cases.[2] The incidence of more subtle effects of hyponatremia on cerebral function in this group of patients is not known.[5]

A number of factors predispose pediatric kidney transplant recipients to the development of acute hyponatraemia postoperatively. Whilst the kidneys maintain electrolyte homeostasis in health, this function is impaired in the post-transplant setting due to changing GFR and ischemic tubular injury. Relatively large volumes of intravenous fluid are used to establish and maintain transplant perfusion intraoperatively[1]. Polyuria is common in the postoperative period, and replacement of urine losses constitutes additional risk of electrolyte disturbance. In addition, non-osmotic release of vasopressin following surgery limits free water excretion. The volumes of intravenous fluid administered in our cohort did not differ significantly between patients with and without postoperative hyponatremia. The high incidence of hyperglycemia in the study population may have contributed to hyponatremia via an osmotic dilution, however the relatively mild degree of hyperglycaemia (median 1.0mmol/l above the upper limit of normal) suggests that this unlikely to be a significant factor.

The risk of acute hyponatremia is currently mitigated by very frequent plasma electrolyte monitoring, with changes in intravenous crystalloid fluid if abnormalities arise. Whilst this clinical management strategy limits the progression of electrolyte imbalance to serious neurological events

in most cases, delays in blood sampling, laboratory processing, communication of results and corrective action constitute significant postoperative risks.

Immunosuppressive and diuretic medications can exacerbate electrolyte disturbance in pediatric recipients.[6] Our cohort was treated with a standard immunosuppression regimen.

The optimal intravenous crystalloid solution for pediatric kidney transplant recipients remains debated. A survey of all UK pediatric transplant centres' clinical care protocols in September 2018 revealed that 8 (80%) of 10 centres use 0.45% sodium chloride 5% glucose as initial intravenous crystalloid to replace urine losses, with 2 centres using 0.9% sodium chloride as first line intravenous crystalloid (personal communication). The results from the current study are therefore representative of the most commonly utilised intravenous fluid regimen in UK pediatric transplant practice.

A fluid strategy which minimises post-transplant electrolyte imbalance, and thereby the need for fluid prescription changes, is desirable. Hyponatremia is the commonest electrolyte problem in this group of children and can have catastrophic sequelae. Hypotonic solutions such as 0.45% sodium chloride are associated with hyponatremia and neurological sequelae in children.[5,7-10] Hyperglycaemia is a further concern when large volumes of crystalloid containing glucose are administered[11], as experienced by the majority of our cohort. Intravenous 0.9% sodium chloride reduces the risk of hyponatremia, but is associated with hyperchloraemic metabolic acidosis and hyperkalemia in adult kidney transplant recipients.[12-14] Our data confirm that hyperchloremic acidosis is common in pediatric kidney transplant recipients, which may underlie reluctance to administer 0.9% sodium chloride in these patients.[14] Comparison of electrolyte imbalance with the 2 UK centres using 0.9% sodium chloride as first line fluid may be informative, however this was not feasible as their practice changed only recently. Balanced crystalloid solutions reduce hyperchloremic acidosis in adult kidney transplant recipients[12,14], however concerns about their potassium content for children with impaired kidney function have arisen. Further work is needed

to understand the most appropriate crystalloid solution to minimise abnormalities in plasma sodium, potassium and acid-base balance for this group of children.

Our finding of significantly more hyperkalemia in deceased donor transplant recipients is expected; it corroborates data from liver transplant recipients in which hyperkalemia was associated with longer ischemic times.[15] The association of hyperkalemia with hyperchloremic acidosis was previously observed adult kidney transplant recipients [16] and highlights the need to address all electrolyte imbalance in the postoperative period, rather than focussing on single parameters in isolation. The higher incidence of electrolyte imbalance in deceased donor recipients may be related to the significantly lower rate of improvement in eGFR observed in this group in the postoperative period. Longer ischemic times in deceased donor kidneys may result in a greater degree of tubular injury than live donor kidneys, thereby impairing both recovery of GFR and tubular electrolyte handling.

The current data did not show significant differences in overt electrolyte imbalance between smaller (<20kg) and larger (>= 20kg) recipients, however overall plasma potassium concentration was higher and sodium lower in larger children. The rate of improvement in eGFR postoperatively did not differ significantly between smaller and larger recipients, therefore it is unlikely that these electrolyte trends relate to differences in clearance. Similarly, the proportion of live vs deceased donors was similar in both weight groups, and is therefore unlikely to confound electrolyte imbalance. Endogenous factors such as differences in postoperative vasopressin and aldosterone secretion might be responsible for electrolyte differences between weight groups, however these were not assessed in the current study.

This study is limited primarily by its single centre, retrospective design. Nevertheless, the data represent a relatively unselected cohort, as all patients transplanted in the study period were included. In addition, all patients were managed with the most common intravenous fluid strategy used in UK pediatric transplant centres, so are generalizable to a degree. Estimation of GFR is

inaccurate in the context of changing kidney function[17]; we therefore analyzed the rate of improvement in eGFR postoperatively, and relative differences between patient groups were informative. A further limitation was the restricted analysis of factors affecting electrolyte imbalance, as sufficient data on all potential confounders were incomplete. Analyses of donor type and recipient size were feasible and yielded significant results.

In summary, these data confirm that significant electrolyte and acid-base abnormalities are common in pediatric kidney transplant recipients in the postoperative period. Whilst current clinical care strategies mitigate the associated risks of neurological and other sequelae to some degree, further studies to minimise electrolyte imbalances by optimising intravenous fluid therapy in this group of patients are merited.

Conflict of interest

The authors have no conflict of interest to declare.

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Tables

Table 1: Baseline characteristics of cohort. Values expressed as median(range), or number (%). (CAKUT: congenital anomalies of the kidney and urinary tract, SRNS: steroid resistant nephrotic syndrome)

Age (years)	9.9 (2.1 – 17.9)
Weight (kg)	30.1 (10.4 – 85.0)
Native urine output (ml/kg/24 hours)	21 (0 – 270)
Living donor	49 (64%)
Primary diagnosis - CAKUT - SRNS - Glomerulonephritis - Ciliopathies - Metabolic conditions - AKI - Wilms tumour - Unknown	 45 (59%) 12 (16%) 6 (8%) 4 (5%) 3 (4%) 3 (4%) 2 (3%) 1 (1%)

Table2: Comparison of fluid intake and glycemia in patients who experienced hyponatremia vs those who did not. Variables expressed as median (range) or number (%). Statistical comparisons are Wilcoxon rank sum test for continuous variables, and Fisher's exact test for count data.

	Hyponatremia	No hyponatremia	P-value
% weight gain	10.2 (3.8 – 30)	9.3 (0 – 31)	0.6
Fluid intake (ml/kg)			
- Intraoperative	81 (28 – 213)	72 (31 – 149)	0.9
- Day 1	136 (41-283)	125 (73 – 247)	0.8
- Day 2	89 (25 – 200)	106 (44 – 173)	0.3
- Day 3	67 (23 – 246)	86 (27 – 257)	0.1
- Total	390 (122 – 746)	440 (201 – 669)	0.4
Hyperglycemia	44 (98%)	30 (94%)	0.2

Table3: Comparison of eGFR and electrolytes by donor type and recipient size. Variables expressed as median (range) or number (%). Statistical comparisons are Wilcoxon rank sum test for continuous variables, and Fisher's exact test for count data. (eGFR: estimated glomerular filtration rate, AG: anion-gap)

	Donor type			**Recipient size**		
Parameter	**Deceased donor (n =22)**	**Living donor (n = 54)**	**Comparison p**	**< 20kg (n = 17)**	**>= 20kg (n = 59)**	**Comparison p**
eGFR (ml/min/1.73m2)	47(8 - 101)	79(9 - 150)	<0.0001	35(7 - 150)	23(5 - 150)	<0.0001
Slope eGFR (ml/min/1.73m2/day)	11(0.7 – 29)	20(0.3 – 46)	0.001	29(0.3 – 46)	16(0.7 – 37)	0.14
Plasma [Na] (mmol/l)	139(128 - 151)	138(130 - 166)	0.06	144(131 - 155)	138(128 - 166)	<0.0001
Hyponatremia	10(46%)	34(63%)	0.25	7(41%)	37(63%)	0.17
Plasma [K] (mmol/l)	4.6(3.2 - 7.0)	4.3(2.8 - 7.0)	<0.0001	4.1(2.8 - 6.5)	4.4(3.3 - 7.0)	<0.0001
Hyperkalemia	7(32%)	11(20%)	0.003	3(18%)	20(34%)	0.24
Plasma [Cl] (mmol/l)	106(93 - 116)	105(95 - 124)	0.08	110(95 - 119)	105(93 - 124)	<0.0001
Plasma [HCO3] (mmol/l)	21(11 - 30)	22(13 - 32)	0.0006	21(11 - 32)	22(12 - 30)	0.02
Non-AG acidosis	16(72%)	25(46%)	0.17	11(65%)	35(59%)	0.8

Figure legends

Figure 1: Proportion of 76 patients with electrolyte imbalance in the first 72 hours post-transplant

Figure 2: Plasma electrolyte distribution in the first 72 hours post-transplant for deceased donor and living donor transplants. Significance values show Wilcoxon comparison of electrolyte distribution per donor type. Dashed lines show laboratory reference ranges.

Figure 3: Plasma electrolyte distribution in the first 72 hours post-transplant for small (< 20kg) vs larger (>= 20kg) transplant recipients. Significance values show Wilcoxon comparison of electrolyte distribution per recipient weight. Dashed lines show laboratory reference ranges.

Figure 4: Comparison of the rate of change of eGFR during the first 72 hours post-transplant by donor type and recipient size