

A Prospective, Randomized, Controlled Study Comparing the Effects of Normal Saline versus Plasmalyte as Intravenous Fluid on Acid-Base (Base Excess) and Electrolyte Status during Renal Allografting

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Conflict of interest: Nil

Abstract:

Background: The study was conducted to analyze and evaluate the effects of Normal Saline (NS) and Plasmalyte (PL) on acid-base status (Base Excess) and other electrolyte status during renal allografting.

Methods: This prospective, randomized, comparative study included 70 patients who were randomized into two equal groups: Group 1 (NS, n=35) and Group 2 (PL, n=35). Arterial blood samples were collected at five different time points: just before induction of anesthesia (T₀), 30 minutes after induction (T₁), during anastomosis (T₂), at the time of drain insertion (T₃), and 6 hours post-surgery (T₄). The samples were analyzed for pH, PCO₂, PO₂, Base excess (BE), HCO₃⁻, Na⁺, K⁺, Cl⁻, and lactate.

Results: The NS group showed a statistically significant decrease in pH and base excess (BE) and a significant increase in serum chloride levels during the procedure. Specifically, the BE values for the NS group significantly decreased from T₂ (-5.93 ± 1.8) to T₃ (-7.66 ± 1.13) and T₄ (-6.84 ± 1.51), while the PL group's BE remained relatively stable. The mean chloride levels were significantly higher in the NS group compared to the PL group intra-operatively. In contrast, the Plasmalyte group maintained a more stable acid-base and electrolyte balance.

Conclusion: The administration of Normal Saline during renal allografting is associated with the development of significant hyperchloremic metabolic acidosis. This study concludes that Plasmalyte is a superior intravenous fluid choice for maintaining acid-base balance during renal transplantation as compared to Normal Saline.

Keywords: Renal Allograft, Intravenous Fluids, Base Excess, Hyperchloremic Acidosis.

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Introduction

Renal transplant is a surgical procedure that places a healthy kidney harvested from live or deceased donor in a person with diseased kidneys that are no longer functioning. Patients requiring renal transplantation are the ones presenting with End Stage Renal Disease (ESRD), which is the last stage of chronic kidney disease (CKD), where the decline in glomerular filtration rate (GFR) is less than 15ml/min/1.73 m² or the kidney functions are limited to 10-15% of their normal function.

A marked decline in glomerular function in ESRD patients has metabolic effects like acid base and electrolyte disturbance. Acid base balance is normally maintained by renal excretion of daily acid load, derived mostly from generation of sulfuric acid during the metabolism of sulfur containing amino acids [1]. Elimination of this

acid load is achieved by urinary excretion of hydrogen ions. In CKD there is failure of adequate excretion of various acid anions due to greatly reduced number of normally functioning nephrons. As a result, CKD leads to retention of hydrogen ions. The diseased kidneys are unable to maintain acid-base hemostasis resulting in metabolic acidosis which is a common complication encountered with progressive loss of kidney function. Similarly the ability of kidney to excrete potassium also decreases leading to hyperkalemia which can have life threatening cardiovascular manifestations.

The success of any renal transplantation surgery is determined by an optimum functioning graft as early as possible after the completion of surgery. Delayed graft function is grossly defined by the

need for dialysis in the first week post-transplant [2]. One of the reasons for graft failure after renal transplantation is inadequate graft perfusion caused by mismanaged peri-operative hydration strategy. The choice of a particular fluid to be given intra-operatively in a clinical situation is guided by the proper understanding of the solution's properties. The intra-venous administration of adequate volumes of fluid is associated with earlier onset of graft function, declining post-operative serum creatinine levels, improving post-operative creatinine clearance, reduced incidence of delayed graft function, improved chances of graft survival.

Crystalloids are fluids that contain water and electrolytes. They are clear fluids, particle size $<1\mu$, expand the interstitial volume rather than plasma volume. They are grouped as isotonic, hypertonic and hypotonic salt solutions. Isotonic crystalloid solutions, such as 0.9% Saline solution and Ringer Lactate solution, are the first choice for volume restoration and for correcting hemostatic imbalance.

Patients who were randomly assigned to balanced solutions when compared with those receiving saline based fluids, showed enhanced gastric perfusion and preserved renal function. [3]

The aim of our study was to analyze and evaluate the effects of Normal Saline and Plasmalyte an acid base status (Base excess) and other electrolytes status during renal allografting.

Material and Methods

This prospective, randomized study was conducted in the operation theatre and post- kidney transplant care unit and in patient wards of Medanta-The Medicity, Gurgaon and had been completed within a period of one and half years (January 2015 to May 2016) after approval from the ethical committee. Written and informed consent was obtained preoperatively from all the patients after due explanation of the study procedure. As per hospital policy all drugs used and events that occurred peri-operatively were recorded manually and a copy of pre-operative assessment and anesthesia notes written by the concerned consultant anesthesiologist has been preserved.

Sample-size was calculated with the help of statistician. This was based on confidence level of 95% and 80% power. 70 patients were randomized into two equal groups by use of computer based software programme. The sequence of random numbers was kept in the opaque sealed envelopes in which the serial numbers were written on the envelopes and the group to which the subjects at that serial numbers were mentioned inside the envelope. Thus, after recruitment of the patients and taking their consents, the allocation of sample

to two groups was based on the sequence of random number kept in opaque envelopes

Study Design: Prospective, randomized comparative study

Inclusion Criteria: All patients with end stage renal disease admitted for renal transplantation providing consent for participation in the study.

Exclusion Criteria:

- Patients younger than 18 years of age.
- Hyperkalemia; defined as serum potassium exceeding 5.5 mmol/L preoperatively.
- Cadaveric kidney transplantation.
- Pre-emptive renal transplantation.
- Robotic renal transplantation.
- ABO incompatible renal transplantation

Methodology: Pre-operative assessment of the patients was done by taking history, doing physical examination and laboratory investigations that includes Complete Blood Count (CBC), Liver Function Test (LFT), and Kidney Function Test (KFT), Serum electrolytes (sodium, potassium, chloride, and bicarbonate), Blood grouping and typing. The study procedure was explained to the patients before the surgery and a written informed consent was taken.

A baseline arterial blood sample was taken for acid base analysis (that included pH, PCO_2 , PO_2 , Base excess, HCO_3^- , Na^+ , K^+ , Cl^- , lactate) and was recorded in the observation table.

The patients were premedicated with Tab. Alprazolam 0.25 mg and Tab. Pantoprazole 40 mg 2 hours prior to surgery. The technique of anaesthesia was standardized for all the patients in both the groups. Routine monitoring of the patients was done using pulse oximeter, non-invasive BP and ECG. Before induction of anesthesia, peripheral venous access was secured in the hand opposite to the functioning fistula by an 18-G IV catheter and a 20-G arterial cannula.

After pre-oxygenation, general anesthesia was induced using Propofol (2mg/kg), Fentanyl (2mcg/kg), and neuromuscular blockade was done by Atracurium (0.60 mg/kg).

After intubation and confirmation of ETT, the patients were put on mechanical ventilation. Anesthesia was maintained with isoflurane 1-2% in an oxygen-air mixture at 1:1 ratio; maintained at 1 L/min. Additional doses of Fentanyl and Atracurium as infusion were administered as appropriate.

USG guided Central venous catheter was inserted under all aseptic precautions in the Internal Jugular Vein after induction of anesthesia in the right or left side (Depending on the presence of dialysis catheter). Intravenous fluids (as per the group to

which patient was allocated) was given at a rate of 10 - 20 mL/kg/ hr to maintain a targeted CVP of 12–15 mm Hg, and the total volume of fluids was recorded. Each recipient was given methylprednisolone 500mg at the time of anastomosis, and was placed on the same immunosuppressive protocol postoperatively. Intra-operative monitoring included the patient's temperature, EtCO₂ (to be maintained at 35–40 mm Hg), Heart rate, Blood Pressure (invasive/non-invasive), Oxygen saturation and electrocardiogram. The Arterial Blood Gas (ABG) analysis machine was ensured to be calibrated every morning by 8.00 am and the blood samples were analyzed only after the calibration.

Arterial blood samples were collected for acid-base analysis (including pH, PCO₂, PO₂, Base excess, HCO₃⁻, Na⁺, K⁺, Cl⁻, lactate) at Just before induction of anesthesia, 30 minutes after induction, during anastomosis at the time of drain insertion. Use of inotropes or vasodilators were recorded and noted down during the procedure. At the end of surgery, study fluid was discontinued; neuromuscular blockade was reversed by Neostigmine 0.05mg/kg and Glycopyrrolate 8mcg/kg. Post-operatively patients were transferred to post kidney transplant care unit. Epidural analgesia was used for providing pain relief to the patients. Post-operatively, arterial blood samples were taken for acid base analysis at: T₄: 6 hours post-surgery, T₅ -Post-operative day (POD) 1 and T₆ - POD-2. Early post-operative graft functions in terms of serum creatinine; urine output and the

need of dialysis (if any) were also noted down and documented in the study.

Statistical Analysis Plan: The analysis has included profiling of patients for both the groups on different demographic and clinical parameters & co-morbidities etc. Descriptive analysis of quantitative data has been expressed as means and standard deviation. Cross tables were generated and Chi-Square test was used for testing of associations. Student t test was used for comparison of individual quantitative parameters between groups. A repeated measures analysis was undertaken to compare the groups with all follow-up observations. P-value < 0.05 is considered statistically significant. SPSS software is used for analysis.

Results

The study population in both the groups was comparable in terms of demographic profile (age, gender, weight and height), and comorbidities.

The baseline vital parameters (Blood Pressure, Heart rate and Respiratory Rate) and the baseline investigations (Complete Blood Count, Kidney Function Tests) including all parameters of Baseline Arterial Blood as parameters were also comparable in both the groups in the study.

A significant reduction in pH (acidosis) was observed in Group-1 intra- operatively at T₁, T₂, T₃. Which gradually resolved post-operatively and pH showed a rising trend at T₄, T₅, T₆. In group-2 (Plasmalyte) the pH was maintained throughout the study and no acidosis was seen.

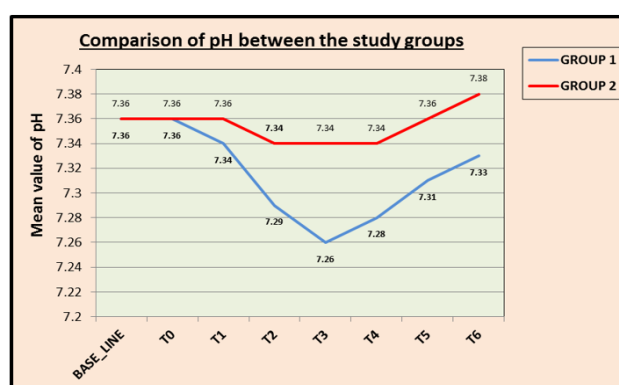


Figure 1: Comparison of pH trend between the study groups at different time points.

Base-excess values for group-1 (Normal Saline) have decreased to a much greater extent as compared to group-2 (Plasmalyte). The differences were significant in T₂ and T₃ intra-operatively.

Post-operatively the BE values were improved once the administration of study fluids was discontinued. However the differences were still significant postoperatively T₄, T₅, T₆.

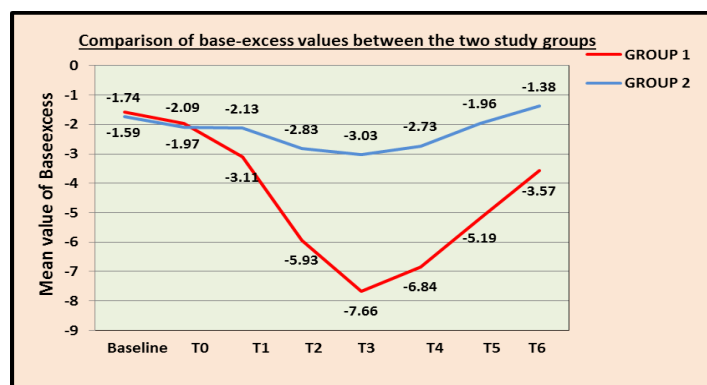


Figure 2: Comparison of base-excess trend between the study groups at different time points.

Bicarbonate levels showed a declining trend in the Group 1 (Normal saline) intra-operatively mainly at T₁, T₂ and T₃ improved post-operatively at T₄, T₅, T₆. In contrast HCO₃⁻ in Group-2 (Plasmalyte) showed a consistent trend throughout the study without showing any significant declining trend. Potassium levels in group-2 (PL) showed a rising

trend intra-operatively (T₂ and T₃) as compared to baseline K⁺ levels not accounting for hyperkalemia and declined in the post-operative period T₅ and T₆ (POD-1 and POD-2 respectively). K⁺ levels for group-1 patients were relatively consistent throughout the study and comparable to baseline K⁺ levels.

Table 1: Independent Student t – test for comparison of mean values of Potassium (K⁺) levels at different time points between the study groups

K ⁺	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean Difference	Std. Er- ror of Mean Difference	95% Confidence Interval of the Mean Difference		t-value	p- value
					Lower	Upper		
BASE LINE	4.40 ± 0.47	4.43 ± 0.46	- 0.0343	0.1108	- 0.255	0.187	- 0.309	0.758
T0	4.33 ± 0.49	4.29 ± 0.45	0.1026	0.1123	- 0.122	0.327	0.913	0.364
T1	4.35 ± 0.47	4.30 ± 0.51	0.0497	0.1175	- 0.185	0.284	0.423	0.673
T2	4.31 ± 0.50	4.48 ± 0.54	- 0.1677	0.1251	- 0.417	0.082	- 1.341	0.184
T3	4.31 ± 0.50	4.63 ± 0.56	- 0.3163	0.1259	- 0.567	-0.065	- 2.513	0.014*
T4	4.31 ± 0.46	4.57 ± 0.57	- 0.2689	0.1235	- 0.515	-0.022	- 2.177	0.033*
T5	4.30 ± 0.37	4.29 ± 0.58	0.0143	0.1161	- 0.217	0.246	0.123	0.902
T6	4.32 ± 0.42	4.14 ± 0.57	0.1794	0.1188	- 0.058	0.417	1.510	0.136

There was not much significant difference in sodium and lactate levels in both the groups and the comparable levels were maintained throughout the study. Intra-operatively group-1(Normal Saline) has shown hyperchloraemia with chloride levels

showed a rising trend at T₁, T₂, T₃ and declined in the post- operative period.

Chloride levels in Group-2 (Plasmalyte) have shown a relatively consistent trend throughout the study.

Table 2: Independent Student t – test for comparison of mean values of chloride (Cl⁻) levels at different time points between the study groups.

Cl ⁻	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Mean Dif- ference	Std. Error of Mean Difference	95% Confidence Interval of the Mean Difference		t-value	p-value
					Lower	Upper		
Base Line	98.86 ± 3.59	101.11 ± 3.12	-2.26	0.80	-3.862	-0.652	-2.806	0.007*
T0	100.66 ± 3.74	101.89 ± 3.08	-1.23	0.82	-2.862	0.405	-1.501	0.138
T1	103.63 ± 3.8	102.00 ± 2.97	1.63	0.81	0.003	3.255	1.999	0.050*
T2	108.80 ± 3.45	103.31 ± 2.73	5.49	0.74	4.003	6.969	7.382	<0.0001*
T3	112.46 ± 3.17	103.14 ± 3.14	9.31	0.76	7.807	10.822	12.331	<0.0001*
T4	111.43 ± 2.72	103.17 ± 3.62	8.26	0.69	8.136	10.892	1.818	<0.0001*
T5	109.26 ± 2.05	102.39 ± 3.4	6.86	0.671	5.52	8.206	10.221	<0.0001*
T6	105.71 ± 2.08	100.91±3.28	4.80	0.656	3.491	6.109	7.319	<0.0001*

Post-operative graft functioning was evaluated in terms of urine output, creatinine levels and need of dialysis. Urine output and creatinine levels on POD-1 and POD-2 were comparable in both the groups and no patient in any group required dialysis in the study. It implies that acid-base disturbances exacerbated by Normal saline administration did not influence graft function. Both the fluids maintained the safety profile of the transplanted kidney.

There were no major complications in the study

Discussion

This prospective, randomized study has shown that Normal Saline administration, as compared to Plasmalyte has worsened the acid-base status by causing metabolic acidosis with a significant reduction in pH and base- excess chiefly in the intra-operative period during live donor kidney transplantation surgery. The acidosis seen in patients with Normal Saline group is associated with hyperchloraemia rather than dilutional metabolic acidosis.

The metabolic acidosis after administration of large volumes of Normal Saline can be caused by two underlying mechanisms- Dilutional acidosis and Hyperchloremic acidosis.

First, dilutional acidosis can result from dilution of extracellular bicarbonate by large volumes of bicarbonate free fluid, or dilution of strong ion concentrations by change in free water content. Serum Na⁺ levels are decreased in dilutional metabolic acidosis.

On the other hand, Hyperchloremic acidosis results from hyperchloraemia [4,5].

It has been demonstrated that the base excess may be manipulated by fluid resuscitation. Generating a hyperchloremic metabolic acidosis will create a spuriously more negative base deficit (or increased base excess) as the Cl⁻ decreases the pH unaccompanied by hypoperfusion and lactic acidemia⁶.

In our study, serum Na⁺ levels were not significant when compared between the two study fluids throughout the study period. In contrast Cl⁻ levels were significantly higher in the Saline group compared to the Plasmalyte group intra-operatively chiefly after the anastomosis or post-perfusion where large amount of Normal Saline was administered intra-operatively suggesting hyperchloraemia as the underlying cause for the metabolic acidosis. The differences between chloride levels for both study fluids were comparable even in the Post-Kidney Transplant care unit. Such a significant rising trend in Cl⁻ levels has not been observed after large volume administration of Plasmalyte. The results are

consistent with several previous studies that demonstrated hyperchloremic metabolic acidosis after Normal Saline administration [7-9]. Three studies performed during kidney transplantation also showed that administration of Normal Saline during kidney transplantation is associated with more severe metabolic acidosis as compared to ringer lactate or Plasmalyte [10-12]. It has been studied that relatively small volumes of saline (30 ml/kg/h) produce a hyperchloremic acidosis with this acidosis derived from the hyperchloraemia & not from other causes [13-16]. The nature and longevity of the acidosis has been described by Bruegger [17] and colleagues in our study, once the Normal saline is discontinued, Cl⁻ levels showed a decline in patients in Post-Kidney transplant Care unit which is consistent with the study done by Waters and Bernstein [18] in which hyperchloremic acidosis was only evident upto 210 minutes after infusion.

Though infusion of Plasmalyte has shown a minimal rising trend in the Potassium levels intra-operatively but hyperkalemia was not seen in any of the patients who received Plasmalyte. The mean peak potassium levels were observed to be 4.63 in Plasmalyte group at T3 during the study.

Our results suggested that intra-operative use of Normal Saline during uncomplicated living donor kidney transplantation did not affect early post-operative kidney functions even though some previous studies have demonstrated that hyperchloraemia can cause renal vasoconstriction with decreased urine output [19-21].

Conclusion

Both Normal Saline and Plasmalyte can be safely used in patients undergoing uncomplicated living donor kidney transplantation. However we observed that Plasmalyte was associated with more physiologic metabolic profile in terms of acid-base and electrolyte balance especially after the anastomosis are done during the surgery or post-perfusion period.. Normal Saline should be used cautiously in kidney transplant recipients who present pre-operatively with metabolic acidosis.

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