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# Effect of normal saline, normal saline with kabilyte (1:1) and kabilyte alone on perioperative outcome in renal transplant recipients

[1.]Dr. Lunat Ayaz *(corresponding Author 3rd year resident MGH jaipur)*
[2.]Dr.(Mrs) Durga Jethava
[3.]Dr.Vipin K. Goyal
[4.]Dr.Birbal Baj
[5.]Dr.Ganesh Nimje

***Abstract:***
*Background: Renal transplantation is a moderate risk surgical procedure. Perioperative outcome is affected by multiple factors, among which role of fluid management is a major contributor. Kabilyte has composition similar to plasma and has shown beneficial effect in major surgeries.*
*Methods: This prospective study enrolled ninety patients, aged 20-60 years undergone live related renal transplantation. Patients were divided in three groups depending on intraoperative crystalloid infused [Group NS: normal saline, Group KL: kabilyte, Group NS+KL: normal saline and kabilyte (1:1)]. All patients were administered crystalloids under pulse pressure guidance and intraoperative changes in acid-base parameters and postoperative urine output, serum creatinine and renal complications were recorded.*
*Results: Demographic variable and preoperative data were comparable in all groups. We observed significant metabolic acidosis (decreased pH and bicarbonates, increased base excess and lactate) and hyperchloremia in normal saline group in compare to kabilyte group. Also, 24 hours urine output was better in kabilyte group in compare to normal saline group. [14.09±3.89 vs 11.79±4.08 (p=0.019)], with no incidence of delayed graft functioning. Postoperative serum creatinine on day 1, 2 and 5 was similar in all study groups.*
*Conclusion: Kabilyte is better crystalloid than normal saline in renal transplant surgeries in term acid-base and electrolyte balance and renal outcome (urine output and DGF).*

***Keywords:*** *End-stage renal disease, acid-base analysis; normal saline, delayed graft functioning, renal transplantation*

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## I. Introduction

Chronic kidney disease (CKD), is defined as structural or functional abnormalities of the kidneys for >3 months irrespective of cause, as indicated by either kidney damage (pathologic abnormalities or presence of markers of kidney damage or abnormalities in the composition of the blood/urine or abnormalities in imaging tests) and/or glomerular filtration rate (GFR) <60 ml/min/1.73 $m^2$.[1-3] Progressive decline in renal function manifested as sign and symptoms related to disturbance of central nervous system (altered mental status, seizures, coma and/or peripheral neuropathy), cardiovascular (hypertension, left ventricular hypertrophy, dilated cardiomyopathy, ischemic heart disease, pulmonary hypertension, arrhythmias and/or pericarditis), pulmonary system (pulmonary edema and/or pleural effusion), gastro-intestinal (anorexia, nausea, vomiting and/or gastric ulceration), hematological (anemia and/or abnormal coagulation), and metabolic (hyperkalemia, hypocalcemia, hypo or hypernatremia, hyperphosphatemia, and/or metabolic acidosis) etc.[4-5]

Irreversible decline in a patient's kidney function, 10-15% of their normal capacity is severe enough to be fatal necessitate for dialysis or transplantation. End-stage kidney disease (ESRD) is defined as an estimated glomerular filtration rate (GFR) less than 15ml per minute per 1.73 $m^2$ body surface area for more than 3 months, or those requiring dialysis an irrespective of GFR.[5] Renal transplantation offers long term survival and improved quality of life for patients with ESRD.

Patients undergoing renal transplantation are subject to a wide variety of perioperative complications due to associated co-morbidities, hemodynamic fluctuations and/or acid-base and electrolyte disturbances. In the perioperative period, intravenous fluid management plays a vital role and aims to maintain an optimal intravascular volume to ensure renal perfusion and maximize immediate graft function.[6] In-appropriate fluid

management may result in poor patient and graft outcome. Hypovolemia can cause delayed graft functioning, acute tubular necrosis and/or need for vasopressors or inotropes, while hypervolemia may results in pulmonary edema, congestive heart failure and/or need for mechanical ventilation.

Traditionally, Crystalloids alone have been used to maintain volume during renal transplantation, carry no infectious risk, and have no specific nephrotoxic effects. Some of the fluids used for hydration and resuscitation contain supra-physiological concentrations of chloride (normal saline), which induce or exacerbate hyperchloremia, metabolic acidosis and hyperkalemia, may cause renal vasoconstriction and decreased glomerular filtration rate, prolong time to first micturition, and/or decrease urine output after major surgeries. Lactated ringer contains potassium and can potentially aggravate hyperkalemia in patients with impaired renal function.[6-7]

Kabilyte (Fresenius Kabi, India) is a sterile, non-pyrogenic isotonic crystalloid solution for intravenous infusion. It is lactate free, double buffering powered with acetate and gluconate and has the same osmolarity as plasma (294mOsm/L). Concentration of chloride (98mEq/L) is similar to plasma (96-106mEq/L).
Hypothesis, behind this study, was lack of studies available in literature on effect of different crystalloids mainly newer low chloride balance salt solutions like kabilyte on metabolic and renal effects in renal transplant surgeries.

## II. Methods

This Prospective, double blind, randomized comparative study was conducted over a period of one and a half years at a teaching hospital. Patients were enrolled, after study plan approval, from institutional ethics committee and written and informed consent from all the patients was taken. Study population included, ninety patients, with American society of anesthesiologists (ASA) status III, aged 20-60 years, scheduled for live donor renal transplantation under general anesthesia. Patients with, severe cardio-pulmonary disease, severe liver disease and/or cadaveric donor transplant were excluded from the study.

Enrolled patients were randomly allocated to any of three groups (30 patients in each group) by computer generated table of random numbers. Patients in group normal saline (NS), group KL (kabilyte) and group NS+KL were administered normal saline, kabilyte and normal saline plus kabilyte (1:1) as intraoperative fluid.

All patients underwent routine preoperative check-up including history, physical examination and detailed cardiopulmonary workup (2D-echocardiography (ECHO), Electrocardiography (ECG), X-ray chest and/or pulmonary function test day before the scheduled date of surgery. Patients were advised overnight fasting and tablet alprazolam 0.5 mg with sip of water early morning. After shifting the patient in the operation theatre, an 18-G Intravenous (IV) cannula was secured in non-fistula arm and crystalloids were started. Standard anesthesia monitors (pulse oximeter, ECG, and non-invasive blood pressure) were attached. Anesthesia was induced with IV propofol 1% (2 mg/kg) three minutes after premedication with IV bolus of fentanyl (3µg/kg) and midazolam 1mg. Trachea was intubated with appropriate size of endotracheal tube following intubating dose of cisatracurium (0.2 mg/kg) and anesthesia was maintained with isoflurane in oxygen-nitrous oxide mixture (40:60) and cisatracurium infusion for muscle relaxation. 20-G arterial cannula was inserted in non-fistula arm and invasive blood pressure was recorded continuously. Central venous catheter was placed in internal jugular vein on either side under ultrasound guidance. IV crystalloids were administered at a rate of 5ml/kg/hour with intermittent boluses to maintain pulse pressure variation (PPV) ≤13%, and total volume of fluids infused were recorded. In intraoperative period, the patient's temperature was kept ≥ 36°C and end tidal carbon-dioxide (etCO2) was maintained between 35-40 mm Hg. Intraoperative hemodynamics (mean arterial pressure, heart rate and pulse pressure variation) were recorded throughout surgery as per study protocol and any complication (hypotension or hypertension, arrhythmias, desaturation etc.) were recorded. Arterial blood was sent for acid-base and gas analysis (ABG) after induction of anesthesia (T1) and at the end of surgery (T2). ABG parameters [blood pH, bicarbonate, lactate, sodium, potassium and chloride] were recorded. After extubation, patients were shifted to the renal transplant unit for postoperative care. In the postoperative period, first 24 hour urine output, serum creatinine at day 1, day 2 and day 5 were recorded. Any postoperative complication like delayed graft functioning (need of dialysis within a week of transplant), acute tubular necrosis (increasing creatinine value), pulmonary oedema and mechanical ventilation etc. were recorded.

Patients data were entered into Microsoft excel spread sheet for statistical analysis, and then analysed using SPSS (version27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Demographic and clinical related variables were presented as frequency (percentage), mean ± standard deviation (SD) or median ± interquartile range (IQR) as appropriate. Group comparisons were made using independent t-test as per the distribution of the data for continuous variables. P value <0.05 was considered statistically significant.

## III. Results

This comparative study enrolled ninety patients of ESRD, posted for renal transplantation under general anesthesia. Mean age, weight and height of patients in all groups were comparable and statistically non-significant. Male preponderance over female was seen in all three groups. (Table 1)

Duration of CKD and hemodialysis were (median ± IQR) comparable in all study groups and were statistically non-significant. Preoperative laboratory values (hemoglobin, hematocrit, plasma glucose, serum urea and creatinine) were similar and shown statistical non-significance. Left ventricular ejection fraction on 2-D ECHO was similar in all patients. Average duration of anesthesia was approximately 2 hours (90-140 minutes). Total amount of crystalloids administered in intraoperative period was 2144.67 ± 685.71, 1853.33 ± 890.85 and 1540 ± 452.27 ml in NS, NS+KL and KL groups respectively and was significantly higher in NS group. No patient in any group was given colloids (starch or albumin) (Table 2)

Intraoperative mean arterial pressure and heart rate at baseline, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes after induction were comparable in all three groups. Also, the pulse pressure variation after placement of arterial cannula at different intervals was similar in all study groups.

**ACID-BASE AND GAS PARAMETERS**

In normal saline group, changes in ABG values (pH, serum sodium, serum chloride, bicarbonates and lactate) from baseline (T1) to end of surgery (T2) were statistically significant except serum potassium level. (Table 3) In kabilyte group, there were no significant changes in ABG values from T1 to T2 were observed. (Table 4) In normal saline + kabilyte group, there was statistically significant changes in pH, lactate and bicarbonate were noticed. Changes in other values were statistically non-significant. (Table 5)

First 24 hours urine output (Liters) in kabilyte group was higher (14.09±3.89) in compare to normal saline (11.79±4.08) and normal saline + kabilyte groups (11.6±3.15) and was statistically significant (p=0.019). Level of serum creatinine on postoperative day 1, 2 and 5 were similar in all three groups and was statistically non-significant. Delayed graft functioning was seen in 2 (6%), 0 and 1 (3%) patients in NS, KL and NS+KL groups respectively. Acute tubular necrosis was not seen in any patient. (Table 6)

## IV. Discussion

Perioperative intravenous fluid therapy has been a much neglected area of clinical practice and suboptimal prescribing has often resulted in morbidity and even mortality. A balance electrolyte solution has the physiological electrolyte pattern of plasma in terms of sodium, potassium, calcium, magnesium, chloride, and their related contributions to osmolality, as well as bicarbonate or other metabolizable anions to establish a physiological acid-base balance.[8-12] Infusion of such a balanced solution is devoid of the risk of iatrogenic disruptions except for potential volume overload.

Isotonic crystalloid solutions, have been the first choice for volume restoration during renal transplantation, but various crystalloid solutions can impact electrolyte and acid-base balance differently.[8-12] 0.9% saline solution remains the most widely used intravenous fluid during the perioperative period, but recent data has emerged questioning its safety. A 0.9% saline solution has been shown to reduce renal cortical blood flow in healthy volunteers, and animal studies have suggested that sustained renal vasoconstriction is specifically related to hyperchloremia.

Kabilyte is a balanced crystalloid solution that closely resembles the composition of human plasma (electrolytes, osmolality and pH). There is a paucity of data assessing the impact of the kabilyte on renal function in patients undergoing renal transplantation.

In our study, we did not observe any significant change in blood pH, lactate and chloride concentration in kabilyte group, as seen in patients who received normal saline and normal saline + kabilyte (metabolic acidosis, increased lactate and hyperchloremia). O Malley and colleagues, compared normal saline and ringer lactate (n=30 in each) in renal transplant patients and concluded that patients given normal saline had hyperkalemia in 19% of cases and metabolic acidosis in 31% cases compared to 0% in the ringer lactate group.[13] Similar results (hyperkalemia and acidosis), in normal saline group was also observed by Khajavi MR et al., in their study in renal transplant patients.[14] Hadimioglu N et al., also published similar study in renal transplant surgery comparing among normal saline, plasmalyte and ringer lactate (n=30 in each) and concluded that best metabolic profile was maintained in patient who received plasmalye.[15] High chloride content in 0.9% saline compared to kabilyte (154mEq/L vs. 98mEq/L), is the main contributor for the intraoperative hyperchloremia. Metabolic acidosis, may resulted from increased chloride and lactate while decrease in bicarbonate ions. No significant change in serum potassium was observed in any study groups. In a meta-analysis, including 237 patients for renal transplant comparing lactated ringer's and normal saline solution concluded that at the end of

surgery, the difference in potassium was not significant (p=0.10), however the pH in the normal saline group was lower. [16]

Hyperchloremic metabolic acidosis, after saline infusion may contribute to decreased splanchnic perfusion, as judged by reduced urine flow and abdominal discomfort in healthy volunteers. Within the clinical range, chloride ions have been found to significantly influence renal vascular resistance. Studies in dogs suggest that hyperchloremia leads to renal arteriolar vasoconstriction by inhibiting the intra renal release of renin and angiotensin II, reducing glomerular filtration and urine output. In our study, we observed that 24 urine output after surgery, was lesser in the saline group in compare to kabilyte group. Postoperative serum creatinine concentration at day 1, day 2 and day 5 was comparable in all three groups. Requirement of dialysis within 7 days after transplant (DGF) was 1, 0 and 1 patients in NS, KL and NS+KL group respectively. SY Kim et al. in their study, on renal transplant recipients, did not observe any significant changes in postoperative graft function (urine output, serum creatinine and graft failure) in normal saline and plasmalyte group.[17] Adwaney A et al, in their study in renal transplant surgery concluded that patients in plasmalyte group had better diuresis and less frequent use of renal replacement therapy early after surgery.[18] Nesseler N et al. and Kolodzie K et al., also reported increased incidence of delayed graft functioning in patients received normal saline and concluded that in deceased-donor kidney transplant recipients, perioperative normal saline infusion volume was linked to DGF. [19-20]

Limitations, of the study were small sample size and extension of study duration due to COVID-19 pandemic. We guided the intraoperative fluid by targeting pulse pressure variation that might be associated with confounding factors (high positive end expiratory pressure, arrhythmias, low tidal volume < 8 ml/kg etc.)

## V. Conclusion

In conclusion, kabilyte has shown decreased incidence of metabolic acidosis, better post-transplant urine output and nil postoperative renal complications. We recommend its routine use in renal transplant surgeries.

**Table1. Demographic variables**

| Variable | NS | KL | NS+KL | P value |
|---|---|---|---|---|
| Age (years) | 35.2±9.47 | 36.47±10.56 | 35.05±10.92 | NS |
| Weight (kg) | 57.33±11.42 | 59.48±10.98 | 59.89±10.83 | NS |
| Height (cm) | 168.87±7.56 | 165.93±6.91 | 166.27±6.23 | NS |
| Sex (M:F) | 27:3 | 26:4 | 24:6 | NS |

NS: normal saline, KL: kabilyte NS: non-significant

**Table2. Pre-operative and intraoperative data**

| Data | NS | KL | NS+KL | P value |
|---|---|---|---|---|
| Duration of CKD (months) | 12 ± 30 | 24 ± 28.75 | 16 ± 18.25 | 0.926(NS) |
| Duration of dialysis (months) | 4± 25 | 3± 63 | 5± 10.25 | 0.352(NS) |
| Hemoglobin (g/dl) | 9.52±1.854 | 9.12±1.79 | 8.92±2.072 | 0.471(NS) |
| Hematocrit (%) | 31.86±18.68 | 27.75±5.22 | 26.93±6.27 | 0.227(NS) |
| Urea (mg/dl) | 126.82±51.84 | 131±47.87 | 120.5±48.23 | 0.710(NS) |
| Creatinine (mg/dl) | 9.84±4.61 | 9.44±4.44 | 11.04±8.07 | 0.555(NS) |
| Plasma glucose (mg/dl) | 114.54±37.78 | 116.95±24.38 | 110.47±30.90 | 0.724(NS) |
| Ejection fraction (%) | 54.33±6.79 | 55.5±6.61 | 55.69±5.782 | 0.678(NS) |
| Intraoperative crystalloids (ml) | 2144.67±685.71 | 1540±452.27 | 1853.33±890.85 | 0.005(S) |
| Duration of anesthesia (h) | 2.03±0.18 | 2.00±0 | 2.00±0 | 0.372(NS) |

CKD: Chronic kidney disease, NS: normal saline, KL: kabilyte

**Table3. Acid-base parameters in normal saline group**

| ABG values (mean ± SD) | T1 | T2 | P value |
|---|---|---|---|
| pH | 7.36±0.05 | 7.32±0.04 | 0(S) |
| Sodium($Na^+$) | 133.20±4.14 | 135.23±5.07 | 0.038(S) |
| Potassium($K^+$) | 4.40±.58 | 4.25±0.69 | 0.111(NS) |

| | | | |
|---|---|---|---|
| Chloride($Cl^-$) | 103.37±4.35 | 108.97±5.26 | 0(S) |
| Lactate | 3.96±3.62 | 7.17±7.94 | 0.04(S) |
| Bicarbonate($HCO_3^-$) | 23.12±2.25 | 20.24±0.31 | 0(S) |

T1= after induction of anesthesia T2 = at the end of surgery

**Table4. Acid-base parameters in kabilyte group**

| ABG values (mean ± SD) | T1 | T2 | P value |
|---|---|---|---|
| pH | 7.35±0.05 | 7.35±0.05 | 0.459(NS) |
| Sodium($Na^+$) | 133.33±2.84 | 133.23±3.28 | 0.783(NS) |
| Potassium($K^+$) | 4.29±0.56 | 4.23±0.78 | 0.57(NS) |
| Chloride($Cl^-$) | 103.90±6.39 | 104.3±4.62 | 0.675(NS) |
| Lactate | 5.51±4.71 | 7.80±7.60 | 0.069(NS) |
| Bicarbonate($HCO_3^-$) | 23.65±3.48 | 23.18±3.41 | 0.179(NS) |

T1: after induction of anesthesia, T2: at the end of surgery

**Table5. Acid-base parameters in normal saline + kabilyte group**

| ABG values (mean ± SD) | T1 | T2 | P value |
|---|---|---|---|
| pH | 7.35±0.04 | 7.33±0.05 | 0.015(S) |
| Sodium($Na^+$) | 133.70±4.19 | 129.63±24.02 | 0.376(NS) |
| Potassium($K^+$) | 4.34±0.63 | 4.81±19.69 | 0.339(NS) |
| Chloride($Cl^-$) | 105.03±3.99 | 104.73±19.63 | 0.935(NS) |
| Lactate | 4.67±4.34 | 7.17±5.02 | 0(S) |
| Bicarbonate($HCO_3^-$) | 23.42±5.44 | 21.83±4.49 | 0.04(S) |

T1: after induction of anesthesia, T2: at the end of surgery

**Table6. Postoperative data**

| | | NS | KL | NS+KL | P value |
|---|---|---|---|---|---|
| Urine output (L) | | 11.79±4.08 | 14.09±3.89 | 11.6±3.15 | 0.019(S) |
| Serum creatinine (mg/dL) | Day1 | 2.26±0.94 | 2.44±1.05 | 2.59±0.43 | 0.43(NS) |
| | Day2 | 1.61±0.94 | 1.62±0.74 | 1.92±1.29 | 0.40(NS) |
| | Day5 | 1.36±1.54 | 1.19±0.46 | 1.42±1.10 | 0.72(NS) |
| DGF | | 2 (6%) | 0 | 1 (3%) | NS |

NS: normal saline, KL: kabilyte

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