Ann Anesth Crit Care . 2019 April; 4(1):e95049. doi: 10.5812/aacc.95049.

Published online 2019 August 28. **Research Article**

Effect of Equal Ringer's Lactate and Normal Saline Solution Infusion Versus Normal Saline on Acid-Base Balance and Serum Electrolytes After Living-Related Renal Transplantation: A Randomized Controlled Trial

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Received 2019 June 07; **Revised** 2019 August 05; **Accepted** 2019 August 21.

Abstract

Background: Hyperkalemia is a common complication of renal transplantation (RT). Normal saline (NS) remains the most commonly used infusion solution during RT to avoid hyperkalemia, but it is associated with hyperchloremic metabolic acidosis.
Objectives: We aimed to study the metabolic profile and renal function in RT patients managed with equal NS and ringer's lactate (RL) solution versus NS alone.
Methods: In this randomized controlled trial, 46 adult patients (17 females and 29 males) undergoing living-related RT were recruited and divided into the two groups according to the IV fluid infusion: NS and RL-NS. Subsequently, patients were evaluated based on arterial blood gas (ABG) test, sodium (Na), potassium (K), blood urea nitrogen (BUN), and creatinine (Cr) before and after RT and 3 and 7-day BUN and Cr.
Results: The mean age of the patients was 44.52 $\pm$ 12.58 years in NS and 45.43 $\pm$ 14.29 years in NS-RL group. There were no significant differences in the demographic and baseline patients' characteristics between the two groups. BUN and Cr were lower in the NS group up to 7 days after RT (all $P < 0.05$). Serum Na was lower in the NS-RL group and serum K was higher in this group significantly ($P = 0.004$ and 0.028, respectively). No significant difference was observed regarding acid-base balance and other ABG measures. No case of hyperkalemia or acidosis was observed after RT.
Conclusions: Our study showed that neither NS nor NS-RL solutions were associated with the risk of hyperkalemia or acidosis after RT; however, renal function was superior in patients receiving the NS infusion.

Keywords: Renal Transplantation, Crystalloids, Normal Saline, Ringer's Lactate, Acidosis, Hyperkalemia, Living Donor

1. Background

The gold standard management of patients with end-stage renal disease (ESRD) is renal transplantation (RT). There is a concern to achieve the best possible outcome following RT via established protective measures, including hydrotherapy due to kidney donor shortage (1, 2). Patients undergoing RT are at risk of a variety of complications, which could influence the outcome of transplantation (3). Maintaining optimal intravascular volume via crystalloids administration is crucial to ensure early renal perfusion and function in these patients (4, 5). Hyperkalemia is a common complication of RT which could occur in 25% - 40% of recipients. It could lead to significant hemodynamic and neurological changes (6). To avoid this condition, the choice of IV fluid for perioperative care has recently received increasing attention (7). Classically, normal saline (NS) has been chosen during the perioperative period RT. This choice has been based on the belief that the use of potassium-containing replacement fluids such as ringer's lactate (RL) could produce hyperkalemia (8). A survey of U.S. kidney transplant centers revealed that NS and NS-based solutions are preferred IV fluids for the administration during RT surgery (9).

However, several papers suggested that the usual need for administration of large volumes of NS in patients undergoing RT, is associated with hyperchloremic metabolic acidosis (10), which may theoretically cause hyperkalemia through an extracellular shift of potassium (K) ions (11).

Furthermore, hyperchloremia may cause vasoconstriction in renal arteries, which could result in decreased urine output (12, 13). In addition, rapid administration of NS in patients with pre-existent metabolic acidosis can exacerbate acid-base imbalances immediately after reperfusion of the kidney (14).

This concept was the basis for the elaboration of several studies during the last decade comparing the use of NS and balanced crystalloid solutions (including potassium in their formulation) during the perioperative period of renal transplantation, which all declared that the development of metabolic acidosis and hyperchloremia more frequently occur via the NS infusion compared to the RL one (3, 4, 7, 9, 15). Nevertheless, the NS remains the most commonly used infusion solution during RT (16).

2. Objectives

According to the evidence and shortcoming of NS infusion in RT patients, it was hypothesized that an equal combination of NS and RL could be effective in maintaining renal function after RT; thus we designed a study comparing the metabolic profile and renal function in RT patients managed with NS-RL solution versus NS.

3. Methods

3.1. Study Design and Setting

This randomized clinical trial study was conducted at the Hasheminejad Hospital in 2017 - 2018. This study was approved by the Institutional Review Board and the Ethics Committee (IR.IUMS.FMD.REC1396.9411174015) of Iran University of Medical Sciences prior to patient enrollment and written informed consent was obtained from all participants. The trial was registered at irct.ir (IRCT20170910036107N4, principal investigator: Mehrdad Mesbah Kiaee, date of registration: 2019-04-10).

3.2. Participants

Forty-six adult patients of either gender, aged 18 - 70 years undergoing living donor RT due to ESRD were included. Exclusion criteria were severe cardiovascular disease (ASA (American Society of Anesthesiology) III and IV), preoperative hyperkalemia of $>$ 5.5 mEq/L, using blood transfusion during RT, metabolic acidosis with pH $<$ 7.2, dialysis after the surgery, the duration of the operation more than four hours, and deceased donor RT.

3.3. Randomization, Patient's Enrolment, and Blinding

Participants who enrolled in the study were randomly classified (using block randomization method) into the 2 groups according to IV fluid infusion: patients in the NS group (n = 23), receiving normal saline solution and those in the NS-RL group (n = 23), receiving equal ringer's lactate and normal saline solution. The physicians responsible for the outcome measures, subjects, and data analysis were blinded to the groups.

3.4. Anesthesia Induction and Renal Transplantation

Before the induction of anesthesia, an 18-gauge intravenous catheter was inserted in all patients for fluid and drug infusion. A 20-gauge arterial catheter was also used to obtain arterial blood samples during the operation. All patients were pre-medicated with 2 μg/kg of fentanyl and 0.03 μg/kg of midazolam. Then general anesthesia was induced by the injection 4 mg/kg of sodium thiopental (16). The donor kidney was implanted in the right or left retroperitoneal space of the recipient with vascular anastomoses to the right or left external or internal iliac artery and vein (9). During the surgery, every half an hour, an arterial sample was taken in order to check for the occurrence of severe metabolic acidosis and hyperkalemia.

Intra-operatively fluids were given based on the hemodynamics to maintain systolic pressure variation (SPV) between 5 - 15 mmHg. Post-operative IV fluid infusion was the same in all of the participants. At the end of the surgery, the patients were reversed with 0.05 mg/kg of neostigmine and 0.02 mg/kg of atropine (16).

3.5. Outcome Measures

Arterial blood samples were obtained to evaluate arterial blood gas (ABG) test at baseline before anesthesia induction and postoperatively for measurement of pH, partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO_3), base excess of the extracellular fluid (BE_{esf}) and base excess (BE). Blood urea nitrogen (BUN), serum creatinine (Cr), sodium (Na), and potassium (K) were also measured before and after RT. The measurement of BUN and Cr was repeated 3 days (72 hours) and 7 days (168 hours) after the transplantation. These outcome measures were used to compare the effectiveness of the two infusion solutions.

3.6. Statistical Analysis

The SPSS statistics software V. 22 (SPSS Inc., Chicago, USA) was used for statistical analysis. The normal distribution of the data was evaluated using Kolmogorov-Simonov test. The parametric and non-parametric data were evaluated by Independent Sample *t*-test and chi-square, respectively. Repeated measures design was used to compare the

variables over time. The significant threshold was considered to be less than 0.05.

4. Results

Forty-six patients were assessed for eligibility. All of the patients met the inclusion criteria. They were divided into two 23-member groups. No participant was lost in the follow-up sessions or during analysis. Thus 23 patients in the NS group and 23 patients in the NS-RL group were analyzed (Consort flow diagram).

4.1. Patient Demographics

As it is noted in Table 1, there were no significant differences in the patients' demographic and baseline characteristics between the two groups (all with $P > 0.05$). The mean age of the patients was 44.52 ± 12.58 years in the NS group and 45.43 ± 14.29 years in the NS-RL group. Moreover, 17 of 46 patients were female (37%) and 29 were male (63%). Of the patients in the NS group, 11 were female and 12 were male. In the NS-RL group, there were 6 female and 17 male patients. Patients' baseline BUN and Cr were 39.22 ± 29.74 mg/dL and 6.90 ± 3.73 mg/dL in the NS group and 29.74 ± 11.31 mg/dL and 6.25 ± 2.07 mg/dL in the NS-RL group, respectively. Serum Na was 139.17 ± 2.77 mEq/L and 137.22 ± 3.15 mEq/L in NS and NS-RL group, respectively, before RT. Baseline K was 4.28 ± 0.70 mEq/L in the NS group and 4.13 ± 0.42 mEq/L in the NS-RL group. Baseline ABG test measurements are indicated in Table 1.

Table 1. Baseline Participants' Characteristics

Characteristic	NS	NS-RL	P Value
No.	23	23	
Age, y, mean (SD)	44.52 (12.58)	45.43 (14.29)	0.750
Sex, No (%)			
Female - 17 (37)	11 (47.8)	6 (26.1)	0.127
Male - 29 (63)	12 (52.2)	17 (73.9)	
BUN, mg/dL, mean (SD)	39.22 (29.74)	29.74 (11.31)	0.878
Creatinine, mg/dL, Mean (SD)	6.90 (3.73)	6.25 (2.07)	0.912
Na, mEq/L, mean (SD)	139.17 (2.77)	137.22 (3.15)	0.080
K, mEq/L, mean (SD)	4.28 (0.70)	4.13 (0.42)	0.375
ABG, mean (SD)			
pH	7.32 (0.08)	7.30 (0.09)	0.299
pCO_2, mmHg	33.96 (8.80)	32.26 (8.61)	0.513
HCO_3, mEq/L	18.55 (6.56)	16.36 (5.87)	0.239
BE_{esf}, mEq/L	-8.31 (5.38)	-9.30 (7.09)	0.596
BE, mEq/L	-7.60 (4.88)	-9.39 (6.42)	0.293

Abbreviations: ABG, arterial blood gas test; BE, base excess; BE_{esf}, base excess of the extracellular fluid; BUN, blood urea nitrogen; HCO_3, bicarbonate; K, potassium; Na, sodium; NS, normal saline; pCO_2: partial pressure of carbon dioxide; RL, Ringer's lactate.

4.2. Outcome Measures

Table 2 demonstrated the course of BUN and Cr changes after RT. As it is shown, BUN was decreased in the patients receiving NS in a 3-day assessment after RT reached to 27.63 mg/dL, meanwhile, in patients in the other group who received NS-RL solution, BUN was increased to 51.22 mg/dL. Evaluation of Cr revealed that in the NS group, serum Cr was decreased throughout the study up to a 7-day follow-up evaluation after the surgery, which reduced to 1.49 mg/dL. Meanwhile, patients' Cr in the NS-RL group, after an incline in the period between before and after surgery, was decreased to 2.95 mg/dL 7 days after RT. The BUN and Cr levels were lower in the NS group compared to the NS-RL group in all times evaluated after RT. These differences were significant as it is shown in table 2 ($P = 0.016$, 0.005, and 0.002 after RT and 3 and 7 days after the operation for BUN, and $P = 0.005$, 0.001 and 0.001 after RT and 3 and 7 days after the operation for Cr).

Table 2. Analysis of BUN and Cr Before and After Transplantation in the NS and NS-RL Groups

Time of Evaluation	NS	NS-RL	P Value
BUN, mean (SD), mg/dL			
Before transplantation	39.22 (29.74)	29.74 (11.31)	0.878
After transplantation	30.57 (11.61)	39.48 (12.51)	0.016
3 days after transplantation	27.63 (15.52)	51.22 (30.01)	0.005
7 days after transplantation	27.91 (11.16)	50.30 (28.87)	0.002
Creatinine, mean (SD), mg/dL			
Before transplantation	6.90 (3.73)	6.25 (2.07)	0.912
After transplantation	5.00 (1.65)	6.66 (2.08)	0.005
3 days after transplantation	2.04 (1.66)	4.34 (3.17)	0.001
7 days after transplantation	1.49 (1.00)	2.95 (2.28)	0.001

Abbreviations: BUN: blood urea nitrogen; NS, normal saline; RL, Ringer's lactate.

The evaluation of serum Na and K is indicated in Table 3. Serum K was increased in both groups after the transplantation, but it was significantly lower in the NS group compared with the NS-RL group (4.31 mEq/L versus 4.87 mEq/L, $P = 0.028$). Serum Na was decreased in the NS-RL group, reaching to 136.78 mEq/L after RT, but this electrolyte was increased to 139.48 mEq/L in the NS group. Therefore, serum Na was lower in the NS-RL group after

surgery which was statistically significant (P = 0.004). Patients' arterial blood was evaluated with ABG test. There were no significant differences between the two groups regarding acid-base balance and other ABG measures, all with P > 0.005 (Table 3). Neither case of hyperkalemia nor acidosis was observed in evaluating the post-operative blood samples.

5. Discussion

The aim of this study was to compare the effect of two different crystalloid IV fluid solutions on ESRD patients' renal function and acid-base and electrolyte balance after living donor RT. This was the first study to evaluate the normal saline-ringer's lactate solution as the choice of IV fluid infusion. In this study, the patients who received normal saline during the operation had lower BUN and Cr, which was preserved up to 7 days after the transplantation. Comparing patients' arterial blood after RT, Na and K change levels were contradictory. Such that lower mean Na level and higher mean K level were observed in the patients receiving NS-RL. Despite these differences, Na and K levels were in the normal range in both groups and hyperkalemia was observed in the patients receiving neither NS nor NS-RL during RT. Regarding changes in ABG, in both study groups, a decrease in pH and bicarbonate levels and an increase in pCO_2 were noted. Even though these changes were slightly higher in the NS group, there was no difference between the two groups and acidosis was not observed in both groups.

Table 3. Analysis of Na, K and ABG Before and After Transplantation in the NS and NS-RL Groups

Score	Before Transplantation	After Transplantation	P Value
Na, mEq/L, mean (SD)			
NS	139.17 (2.77)	139.48 (3.45)	0.004
NS-RL	137.22 (3.15)	136.78 (2.56)	
K, mEq/L, mean (SD)			
NS	4.28 (0.70)	4.31 (0.80)	0.028
NS-RL	4.13 (0.42)	4.87 (0.91)	
ABG, mean (SD)			
pH			
NS	7.32 (0.08)	7.28 (0.09)	0.289
NS-RL	7.30 (0.09)	7.26 (0.07)	
pCO_2, mmHg			
NS	33.96 (8.80)	35.91 (7.49)	0.320
NS-RL	32.26 (8.61)	33.96 (5.54)	
HCO_3, mEq/L			
NS	18.55 (6.56)	15.77 (3.91)	0.583
NS-RL	16.36 (5.87)	15.18 (3.26)	
BE, mEq/L			
NS	-9.60 (4.88)	-9.91 (4.34)	0.516
NS-RL	-9.39 (6.42)	-9.79 (7.13)	

Abbreviations: ABG, arterial blood gas test; BE, base excess; NS, normal saline; HCO3: bicarbonate; K: potassium; Na, sodium; pCO_2: partial pressure of carbon dioxide; RL: Ringer's lactate.

The NS is the first choice for IV fluid infusion during RT, but various crystalloid solutions were studied with different impact on electrolyte and acid-base balance (12). The reason behind the selection of NS as the choice of fluid therapy in ESRD patients during transplantation is to avoid theoretical hyperkalemia caused by potassium-containing crystalloids such as RL (12, 17). However, there is an ongoing concern that the administration of a large amount of NS could lead to metabolic acidosis due to dilutional acidosis or hyperchloremic acidosis (18, 19). Regardless of its reason, the acidosis may be of particular significance in patients with ESRD undergoing RT (9). Several studies supported the hypothesis that NS administration is associated with metabolic acidosis compared to other balanced crystalloids such as RL and plasmalyte (5, 7, 9, 10). In Kim et al. study (5), NS infusion was associated with lower pH and BE, and patients receiving NS during living donor RT showed hyperchloremic rather than dilutional metabolic acidosis. In O'Malley et al. study (9), 31% of enrolled patients in the NS group experienced metabolic acidosis compared to zero patients in the RL group (P = 0.004) and suggested that RL was associated with less acidosis. In a meta-analysis by Trujillo-Zea et al. (10), the pH was lower in the NS group (MD: 0.06; CI 95%: 0.05 - 0.08; P < 0.001; I^2 = 17%) and it was suggested that the NS causes metabolic acidosis, probably as a result of hyperchloremia. In a Cochrane review conducted by Wan et al. (20), the authors suggested that balanced electrolyte solutions are associated with less hyperchloremic metabolic acidosis compared to NS; however, it remains uncertain whether lower-chloride solutions lead to improved graft outcomes compared to normal saline. In Hadimioglu et al. (3) and Kanithi et al. (16) studies, there was a significant decrease in pH, bicarbonate (HCO_3), and BE in NS group compared to RL and plasmalyte, respectively, but no patient developed clinically significant metabolic acidosis. In the present study, patient in neither group developed metabolic acidosis and there was no significant difference between the NS and NS-RL regarding pH, HCO_3, and BE. This could be due to the use of the NS solution in both groups and its effect on acid-base balance.

Hyperkalemia is an important aspect of managing patients undergoing RT. This phenomenon is expected with the RL infusion. An extracellular shift of potassium caused

by acute changes in blood hydrogen concentration after NS administration could be a theoretical mechanism for the development of hyperkalemia, which is related to hyperchloremic metabolic acidosis (11). In our study, although serum K level was higher in the NS-RL group, there was no incidence of hyperkalemia (defined as serum K > 5.9 mEq/L). Similar to our study, Hadimioglu et al. (3) reported no significant changes of K levels in neither NS, RL nor plasmalyte groups. In O'Malley et al. study (9), 19% of patients in the NS group versus zero patients in the RL group had K concentrations > 6 mEq/L (P = 0.05). In Trujillo-Zea et al. study (10), K differences was not significant (means difference (MD: -0.26 mEq/L; CI 95%: -0.58 to 0.05 P = 0.10; I^2 = 75%) between the NS and RL groups. Gonzalez-Castro et al. (8) concluded that the use of balanced crystalloids containing K in the perioperative period of RT does not affect serum K levels more than NS. The difference in the K level in different studies could be due to differences in the surgery duration and volume of fluid taken. It seemed that a shorter duration of surgery and lower total volume of fluids infused is responsible for a lower incidence of hyperkalemia.

Evaluation of day 3 and 7 BUN and Cr demonstrated the higher renal function in patients receiving NS. Comparing NS and RL in Trujillo-Zea et al. meta-analysis (10), no difference was reported in Cr level on the third postoperative day (MD: -0.05; CI 95%: -0.59 to 0.48; P = 0.85; I^2 = 0%). In Modi et al. study (4), 24 hours after the surgery, serum creatinine was 2.43 $\pm$ 0.87 mg/dL in the RL group compared to 2.82 $\pm$ 0.75 mg/dL in the NS group. Mean Cr level on the day 3 of surgery in the Khajavi et al. study (15) was 1.9 $\pm$ 0.7 mg/dL in the NS group and 2.2 $\pm$ 2.2 mg/dL in the RL group (P = 0.425). In several studies, plasmalyte use was associated with the best renal function (2, 6). Adwaney et al. (2) reported better graft function at 3 months postoperatively (estimated glomerular filtration rate 51 versus 44 mL/min/1.73 m^2; P = 0.03) in patients receiving exclusively plasmalyte compared to NS such that no difference was seen in graft function at 1-year comparison. In Weinberg et al. study (6), the more Cr reduction was observed in subjects receiving plasmalyte who did not require dialysis compared to patients receiving NS 48 hours after the surgery (-0.03 (-0.17, 0.10) compared to 0.18 (0.03, 0.34); P = 0.04).

Despite the strength of the present study, which is the first to evaluate the effect of NS-RL solution, it is subjected to a number of limitations. The first was the small sample size and limited follow-up period (7 days). Cadaveric donor renal recipients were excluded from the study while live donor RTs make up 43% of transplantation annually in the United States (21). Important factors such as the duration of surgery and total fluid volume were not recorded, which may influence the outcome, especially serum K level.

5.1. Conclusions

Our study showed that neither of NS or RL-NS solutions were associated with the risk of hyperkalemia or acidosis after RT; however, renal function was superior in patients receiving NS infusion. Though there is no risk of hyperkalemia or acid-base imbalance with NS-RL solution, NS is the IV fluid choice in RT due to the better renal function profile.

Footnotes

Authors' Contribution: Mehrdad Mesbah Kiaee designed the study and observed the accuracy and validity of the study. Sarah Faghfuri collected the data and followed up the study participants. Gholam Reza Movaseghi supervised the project. Mahmoud Reza Mohaghegh Dolatabadi and Masoud Ghorbanlo edited and revised the final manuscript.

Conflict of Interests: No conflicts of interest are declared by the authors.

Ethical Approval: This study was approved by the Iran University of Medical Sciences Institutional Review Board and the Ethics Committee (IR.IUMS.FMD.REC1396.9411174015) prior to patient enrollment and written informed consent was obtained from all subjects participating in the trial.

Funding/Support: No funding or grants or equipment were provided for the project from any source, and there are no financial benefits to the authors.

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