

Normal saline versus balanced crystalloids in patients with prerenal acute kidney injury and pre-existing chronic kidney disease

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Introduction: Normal saline (N/S) and Ringer's-Lactate (L/R), are administered in everyday clinical practice. Despite that, N/S increases the risk of sodium overload and hyperchloremic metabolic acidosis. In contrast, L/R has lower sodium content, significantly less chloride and contains lactates. In this study we compare the efficacy of L/R versus N/S administration in patients with prerenal acute kidney injury (AKI) and pre-established chronic kidney disease (CKD).

Methods: In this prospective open-label study we included patients with prerenal AKI and previously known CKD stage III-V without need for dialysis. Patients with other forms of AKI, hypervolemia or hyperkalemia were excluded. Patients received either N/S or L/R intravenously at a dose of 20 ml/kg body-weight/day. We studied kidney function at discharge and at 30 days, duration of hospitalization, acid-base balance and the need for dialysis.

Results: We studied 38 patients and 20 were treated with N/S. Kidney function improvement during hospitalization and at 30 days after discharge, was similar between the two groups. Duration of hospitalization was also similar. Anion-gap improvement as expressed with Δ anion-gap between discharge and admission day was higher in those patients that received L/R in comparison to those that received N/S and pH increase (Δ pH) was slightly higher in the L/R group. No patient required dialysis.

Conclusions: Administration of L/R or N/S to patients with prerenal AKI and pre-established CKD had no significant difference in short or long term kidney function but L/R showed a better profile in acid-base balance improvement and Cl^- overload in comparison to N/S.

Key words: acute kidney injury, balanced solutions, chronic kidney disease, hyperchloremia, normal saline.

What is new? What is important?

The novel findings of the study include that either L/R or N/S administration for volume restoration in patients with prerenal acute kidney injury and pre-existing chronic kidney disease has a similar effect on kidney function both in the short and in the long term.

Nevertheless, patients that receive N/S show a significant increase in plasma Cl^- concentration while patients that receive L/R show a plasma anion gap reduction.

INTRODUCTION

Acute kidney injury (AKI) is a syndrome characterized by acute reduction of kidney function with consequent electrolyte, fluid and acid-base disorders. Its definition and diagnosis is now standardized and based on sequential elevations of serum creatinine measurements and/or the reduction of urine output, which then are used for the classification of AKI into three stages of increasing severity [1]. AKI is associated with an increased mortality [2], with an increased risk of subsequent development of end stage kidney disease (ESKD) [3] and poses a significant economic burden on health systems [4].

In the consensus of the 22nd Acute Disease Quality Initiative conference it is proposed that the

goal for each patient diagnosed with AKI during hospitalization is the recovery to baseline kidney function in the shortest period with a minimum number of complications [5]. Treatment choices are determined by the nature of AKI i.e. pre-renal, renal or post-renal AKI. In cases where dehydration or low circulatory volume are the prominent causes, the mainstay of treatment comprises of volume expansion and hemodynamic improvement mainly with crystalline solutions. Nevertheless, there is no solid evidence on the optimal composition of crystalline solutions in patients with pre-established CKD. These patients represent a challenging group, as they have pre-existing acid-base and electrolyte disturbances (metabolic acidosis and hyperkalemia respectively) which are further deteriorated by superimposed AKI.

Crystalline solutions and their most common representatives, normal saline 0.9% (N/S) and Ringer's Lactate (L/R), are freely administered for increasing intravascular volume. Normal saline is the most commonly used solution in everyday clinical practice as well as in intensive care medicine. However the high amount of sodium it contains (154 mmol/l) increases the risk of sodium overload. Furthermore, its chloride concentration (154 mmol/l), much higher than chloride concentration in human plasma, can cause hyperchloremic metabolic acidosis [6–10]. In contrast, L/R possesses the advantage of lower sodium and chloride content as well as lower osmolality (273 mOsm/l), while the lactates it contains may be of benefit in cases with AKI or CKD and concomitant acidemia. Despite this, in a recent double-blind randomized controlled trial, the administration of balanced multi-electrolyte solution in preference to N/S in critically ill patients in the intensive care unit (ICU) did not lower the risk of AKI or death among this group of patients [11].

Thus, in this study we investigated the safety and efficacy of a chloride restrictive (L/R) versus chloride liberal (N/S) intravenous fluid administration in patients with prerenal AKI and pre-established CKD.

MATERIALS AND METHODS

This was a prospective open label study. Eligibility criteria were the following: Adults (>18 years) with pre-existing CKD stage III–V (eGFR-CKD/EPI < 60 ml/min/1.73m²) proved by at least two previous consecutive serum creatinine measurements 3 months apart, with prerenal AKI (KDIGO definition Stage I to III) not requiring dialysis in the acute setting [12]. For diagnosis we used clinical assessment, physical examination and signs such as reduced body weight, marked orthostatic decrease in blood pressure with an increase in pulse rate, and lack of jugular venous distention suggestive of a reduction in extracellular fluid volume. Exclusion criteria were the following: Post renal and intrinsic forms of AKI, clinical hypervolemia, signs of congestive heart failure and hyperkalemia (serum K⁺ level > 5.5 meq/l). Post renal AKI was excluded with kidney and urine bladder ultrasonography while heart congestion with chest x-ray examination. Patients were assigned to receive alternately either N/S or L/R solution intravenously at a dose of 20 ml/kg body weight/day. Per os water intake was unrestricted while other forms of i.v. or per os fluids were prohibited. Duration of intravenous fluids treatment was set until discharge or for a maximum of 5 days. Primary end points were the response of kidney function to treatment at discharge as expressed with the difference of eGFR (Δ eGFR) (CKD-EPI) between admission and discharge and the response of pH and plasma chloride concentration at discharge. Secondary end points included the response of kidney function to treatment at 30 days

after discharge, total length of in-hospital stay and serum bicarbonate (HCO₃⁻) improvement.

The study was approved by the local ethics committee on human research of the University Hospital of Patras as a prospective study with a registration number 823/29.1.18, and is in accordance with the Helsinki Declaration as revised in 2000. All participants were informed and signed an informed consent.

Measurements

All blood gas analyses were made using the same blood gas analyzer (ABL 800 FLEX, Radiometer) for pH, PaCO₂ and bicarbonate. Anion gap values were calculated according to the Na⁺ - (Cl⁻ + HCO₃⁻) formula. Serum sodium, potassium, chloride, creatinine and urea levels were measured using central laboratory equipment (ADVIA® 2400 Chemistry System, Siemens).

Statistical analysis

Continuous data are presented as means ± standard deviation (SD). Normality of data distribution was examined with the Kolmogorov-Smirnov test. Simple t-test or Mann-Whitney test (for normally distributed or skewed data respectively) was used for investigating the differences of means between continuous data of L/R and N/S groups. The differences of means between multiple time points in each group, was examined with repeated measures ANOVA and Bonferroni post-hoc test for data with normal distribution or Friedman test and Dunn's post-hoc analysis for skewed data. A mixed effects model was implemented when data were missing between different time points of cases in repeated measures analysis.

A p-value of less than 0.05 was considered statistically significant and all tests were 2-tailed. GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego California, USA) and SPSS for Windows (version 16.0 SPSS Inc. Chicago II, USA) were used for statistical analyses.

RESULTS

In total, of 427 patients assessed, 51 received treatment according to protocol, while only 38 patients (25 men) were included in the final analysis (20 received N/S and 18 L/R). Thirteen patients were excluded due to protocol deviation. Baseline clinical and biochemical characteristics between the two groups did not show significant differences (Table 1). The total i.v. volume that was actually administered and overall fluids received during the first day after admission and during the entire treatment period was similar between groups (i.v. volume for L/R group 1319 ± 399 vs 1155 ± 379.4 ml/24h for N/S group, p=0.2, and total volume (per os and i.v. fluids) for L/R group 3125 ± 881.4 vs 2905 ± 709.1 ml/24h for N/S group for day 1, p=0.56).

Table 1
Baseline clinical and biochemical characteristics

	N/S group	L/R group	p-value
Age (years)	65±13.2	59.6±15.8	0.259
Gender (m/f)	13/7	12/6	0.411
AKI stage			
Stage-I	11	12	0.352
Stage-II	3	4	
Stage-III	6	2	
Cause of pre-renal AKI			
Gastroenteritis	6	4	0.496
Diuretics	9	8	0.937
Other	5	6	0.854
Concomitant medication			
Diuretics (furosemide or hydrochlorothiazide)	14	7	0.101
ACEi/ARB	11	6	0.645
Calcium blockers	13	6	0.226
b-blockers	11	11	0.414
Biochemical parameters			
Pre-admission baseline serum creatinine (mg/dl)	2.18±0.68	2.29±0.99	0.91
Pre-admission baseline eGFR (ml/min/1.73m ²)	30.97±11.04	31.46±10.33	0.888
Serum creatinine at admission (mg/dl)	3.77±1.24	3.57±1.41	0.42
eGFR at admission (ml/min/1.73m ²)	16.85±8.27	18.39±6.74	0.36
pH	7.382±0.098	7.33±0.104	0.22
K ⁺ (3.5–5.5 mmol/l)	4.5±0.86	4.12±0.6	0.12
Cl ⁻ (96–106 mmol/l)	102.1±8.37	105.4±7.42	0.23
HCO ₃ ⁻ (meq/l)	19.61±4.1	17.41±3.87	0.13
Anion gap	11.1±7.69	11.8±4.89	0.76

Table 2

Kidney function as expressed with eGFR, acid base and biochemical values after intervention (N/S or L/R) and in consecutive days after admission

	N/S 0.9% N=20								L/R N=18							
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	p ^a		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	p ^a	
eGFR (ml/min/1.73m²)	16.8±8.4	21.1±13.3	23±15.2	23.8±9.5	25.7±19.4	22.2±13.5	0.05		18.3±6.6	20.6±6.8	23.1±9.1	24.1±8.7	26.9±10.6	29.94±9.7	<0.001	
pH	7.38±0.11	7.35±0.06	7.34±0.07	7.35±0.07	7.39±0.04	7.41±0.08	0.039		7.33±0.1	7.34±0.09	7.35±0.07	7.36±0.06	7.35±0.06	7.38±0.05	0.17	
Cl⁻ (meq/l)	101±8.4	106.3±5.2	107.1±5.8	106.1±6.8	108.4±6.2	108.4±8.1	0.039		103.9±7.9	107.4±5.9	107.9±5.7	109.4±4	109.1±4.5	107.7±5.6	0.07	
Anion gap	11.5±5.3	8.3±2.8	8.6±3.8	7.8±3.2	7.3±3.2	10.6±6	0.2		13.9±3.9	11.2±3.8	9.9±3.7	7.5±4.2	6.1±4.1	7.6±4.3	0.007	
K⁺ (meq/l)	4.5±0.9	4.3±0.5	4.4±0.4	4.1±0.5	4.3±0.3	4.1±0.7	0.09		4.1±0.6	4±0.6	4.1±0.6	4.2±0.4	4.3±0.5	4.1±0.7	0.59	

^a Repeated measures ANOVA or Friedman test with the use of mixed effects model in case of missing values.

Kidney function during hospitalization, at discharge and 30 days after

Kidney function overall improved significantly in both groups. eGFR on discharge was 25 ± 15.78 ml/min/1.73m² in patients that received N/S and 26.83 ± 10.43 ml/min/1.73m² in patients that received L/R (Fig. 1A). There was no significant difference in the degree of eGFR improvement between groups as expressed with Δ eGFR between discharge and admission (Fig. 1B). The course of mean eGFR during hospitalization

showed a constant and significant increase in both groups (Fig. 1C-D, Table 2).

Moreover, kidney function at 30 days after discharge was available for 13 patients in each group. No significant difference was found between the two groups (Fig. 1A). Furthermore, eGFR improvement at 30 days in comparison to admission kidney function between those treated with L/R and N/S showed no differences. Kidney function as expressed with eGFR values after intervention between admission, discharge and 30 days after is presented in Table 3.

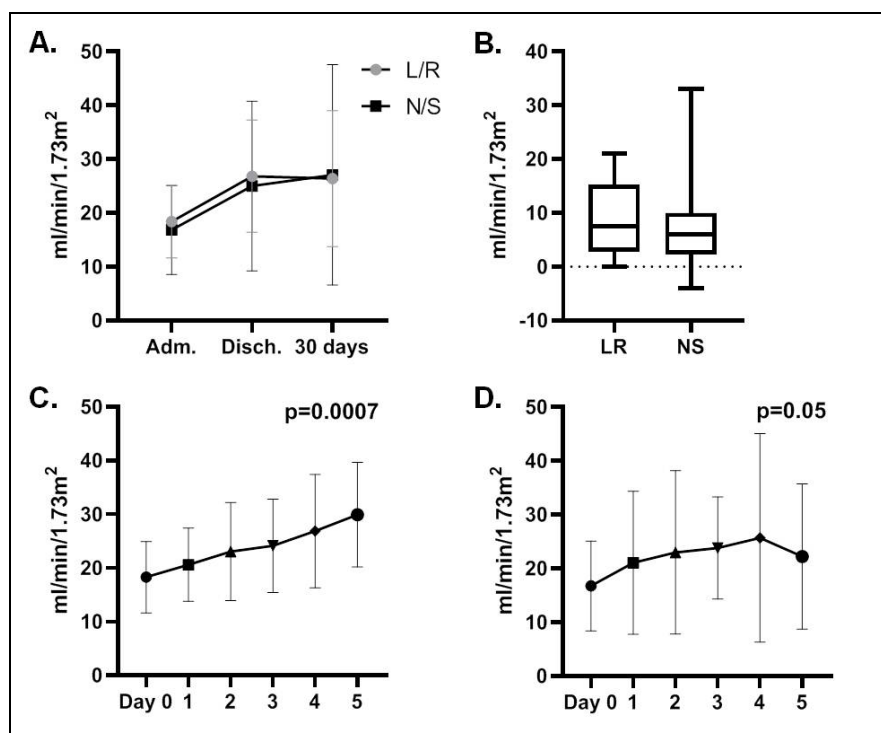


Fig. 1. Course of kidney function as expressed with eGFR (A) during follow up and kidney function improvement at discharge between the two groups as expressed with Δ eGFR (B). Course of eGFR during hospitalization in patients treated with L/R (C) and N/S (D).

Table 3

Kidney function as expressed with eGFR, acid base and biochemical values after intervention (N/S or L/R) between admission, discharge and 30 days after

Parameter	N/S 0.9% N=20				L/R N=18				p ^b	p ^c
	Admission	Discharge	30 d.	p ^a	Admission	Discharge	30 d.	p ^a		
eGFR (ml/min/1.73m ²)	16.9±8.3	25±15.8	27.1±20.5	0.002	18.4±6.7	26.8±10.4	26.4±12.7	<0.001	0.29	0.62
pH	7.38±0.09	7.38±0.06	-	0.38	7.33±0.11	7.37±0.06	-	0.07	0.51	-
Cl ⁻ (meq/l)	102.1±8.4	107.2±6.1	-	0.01	105.4±7.4	108±4.4	-	0.06	0.62	-
Anion gap	11.1±7.7	9.1±4.8	-	0.14	11.8±4.9	7.5±4.9	-	0.006	0.44	-
K ⁺ (meq/l)	4.5±0.9	4.2±0.5	-	0.16	4.1±0.6	4.2±0.7	-	0.58	0.94	-
ΔeGFR (ml/min/1.73m ²)	8.6±9.8		9±13.9	-	8.4±6.4		9.2±9.4	-	0.75	0.34
ΔpH	0.000579±0.102		-	-	0.038±0.072		-	-	0.25	-
ΔCl ⁻ (meq/l)	5.039±8.31		-	-	2.65±5.4		-	-	0.32	-
Δanion gap	-1.98±6.83		-	-	-4.31±4.87		-	-	0.29	-
Hospitalization (days)	6.3±4.14		-	-	5.83±2.99		-	-	0.99	-

^a p-value of the comparison of parameters between admission and discharge within same group of patients. ^b p-value of the comparison of parameters at discharge between N/S versus L/R. ^c p-value of the comparison of parameters at 30 days after discharge.

Acid base profile

Analysis of pH during a maximum 5 days course of treatment in patients that received L/R showed no significant in between days pH alterations. On the contrary, patients that received N/S, showed an overall significant in between days pH change ($p=0.039$). However, patients that received L/R showed a constant trend of increasing pH values in consecutive days after admission while patients that received N/S showed a trend of decreasing pH values at the first 2 days after admission and an increase onwards (Fig. 2A, Table 2).

There was no significant difference in the degree of pH improvement between groups as expressed with Δ pH between discharge and admission (Fig. 2B). Acid base values (pH) after intervention between admission and discharge are presented in Table 3.

Cl⁻ and anion gap

Patients that received L/R showed no significant increase of plasma Cl⁻, while patients that received N/S had a significant and progressive increase ($p=0.0389$

overall, $p=0.016$, $p=0.0028$ and $p=0.025$ between admission day and 1st, 2nd and 4th day of treatment, respectively) (Fig. 3A, 3B, respectively, Table 2).

Plasma chloride concentration was not significantly different at discharge between those treated with L/R and N/S. Nevertheless, chloride increased more in patients that received treatment with N/S in comparison to those treated with L/R (Δ Cl⁻, 5.039 ± 8.31 vs 2.65 ± 5.4 mmol/l, respectively) (Fig. 3C).

Those that were administered L/R showed a significant reduction in plasma anion gap between admission and day 2 ($p=0.022$) and day 4 ($p=0.029$) after admission (Fig. 4A). However, patients that were treated with N/S showed a non-significant anion gap reduction (Fig. 4B, Table 2).

Plasma anion gap was found within normal range in both groups at discharge. However, anion gap improvement as expressed with Δ anion gap between discharge and admission day showed a better trend in those patients that received L/R in comparison to those that received N/S (Fig. 4C, Table 3). Plasma chloride and anion gap values after intervention between admission and discharge are presented in Table 3.

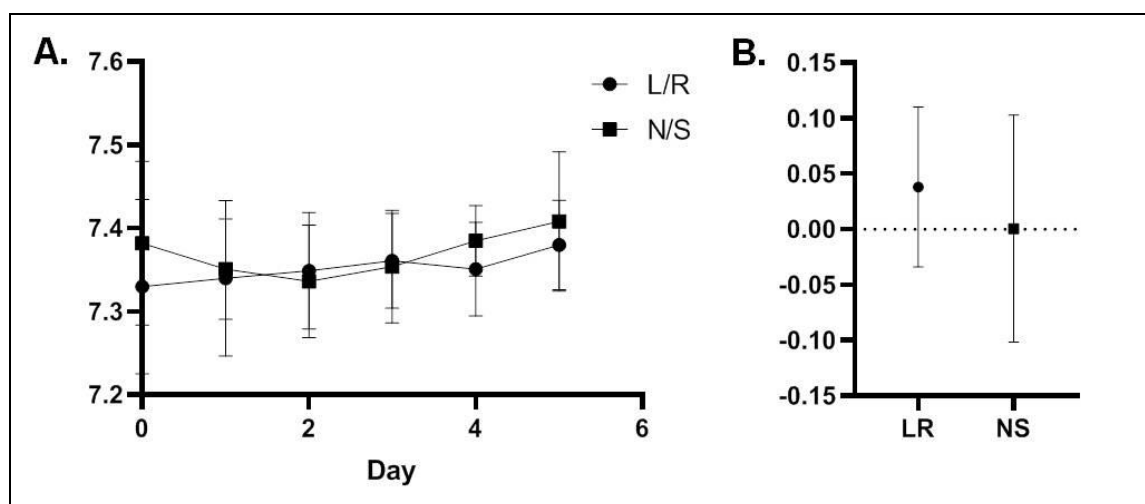


Fig. 2. Course of pH between admission and discharge day (A) and pH improvement as expressed with Δ pH (B).

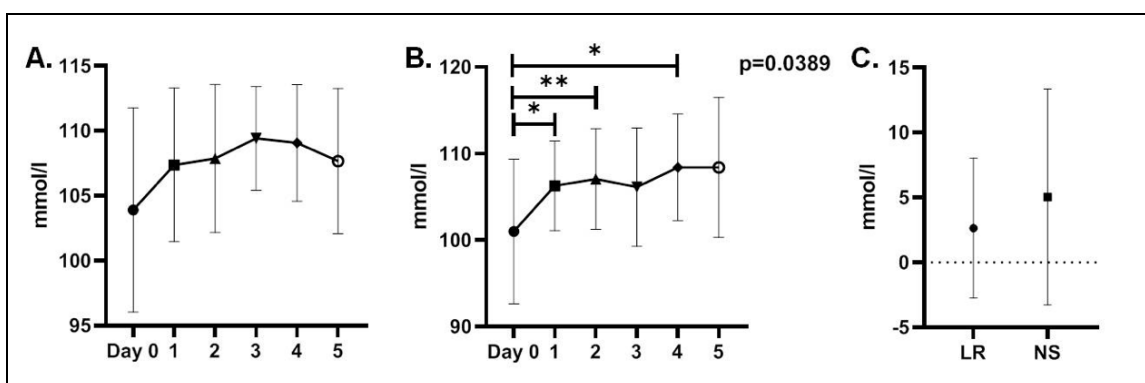


Fig. 3. Plasma chloride concentration during hospitalization in patients that received L/R (A) and N/S (B) solutions. Δ Cl⁻ is presented in (C).

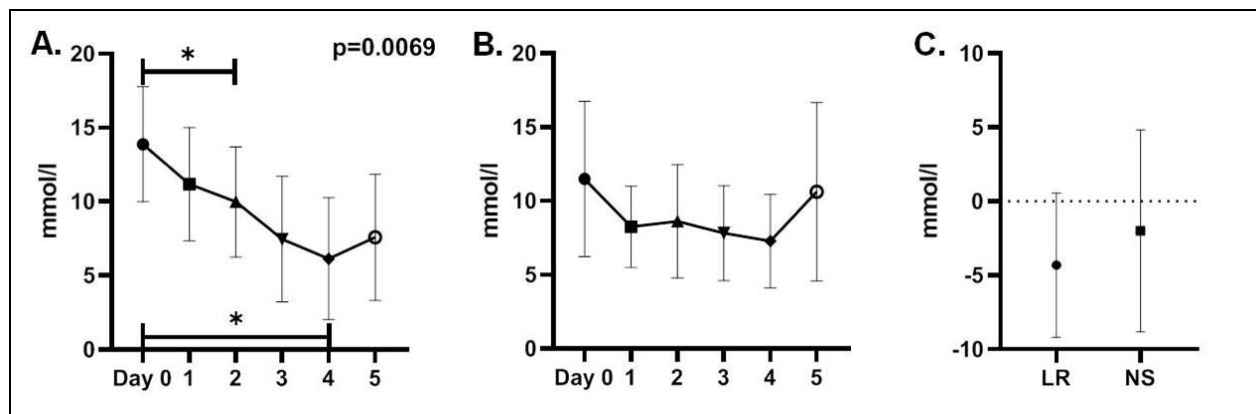


Fig. 4. Anion gap in patients that received L/R (A) and N/S (B) solutions. Δ Anion gap is presented in (C).

Hospitalization

Patients that were treated with L/R had similar hospitalization length in comparison to those that received N/S (5.83 ± 2.99 vs 6.3 ± 4.14 days, respectively).

Adverse events

No patient died during treatment or follow up. Additionally, no patient received dialysis or showed clinical signs of congestion. There were no cases of significant hyperkalemia during treatment.

DISCUSSION

In this study we compared the efficacy and outcomes of two different strategies of fluid administration, a chloride restrictive versus chloride liberal approach in the treatment of patients with pre-renal AKI and pre-established CKD. The novel findings of the study include that either approach has a similar effect on kidney function both in the short and the long term. Nevertheless, there are differences in each approach, as patients that receive N/S show a significant increase in plasma Cl^- concentration while patients that receive L/R show a plasma anion gap reduction.

In every day clinical practice fluid management in critically ill and hypovolemic patients should aim for early restoration of circulatory volume, but it should also be reserved to avoid volume overload. Use of balanced crystalloid solutions versus N/S remains controversial [13]. Nevertheless, chloride concentration of infused fluids is crucial as it can regulate and determine acid-base homeostasis and intracellular volume [14,15].

Kidney function is shown to be affected by the liberal intravenous chloride administration in the set of ICU. In a study of more than 1,500 patients that received liberal chloride therapy, this was associated with a greater risk of AKI [7]. Expanding these observations in the ICU, another study investigated the impact of fluid resuscitation in the emergency department (ED). In this work, patients that received chloride restrictive fluid

resuscitation showed significantly lower rates of kidney injury although they showed no difference in rates of need for renal replacement therapy (RRT) [16]. In an even larger trial, concerning patients treated in the ICU, those that received balanced solutions showed a lower incidence of RRT or persistent kidney dysfunction in comparison to those treated with N/S [17]. In another study, those who were admitted to the ED with kidney dysfunction or hyperchloremia and were consequentially treated outside the ICU with balanced solutions had a significant benefit for avoiding AKI compared to those that were treated with N/S [18]. Nevertheless, there are also studies that demonstrated no benefit by such an approach. In the SPLIT trial on critically ill patients admitted in the ICU, buffered crystalloid fluid therapy compared to N/S did not show any benefit in reducing the risk of AKI or RRT [19]. Moreover, in a recently published trial concerning critically ill patients admitted to the ICU, the administration of balanced multi-electrolyte solution in comparison to N/S, did not lower the risk of AKI or death [11]. In our study, there was no difference concerning kidney function outcomes both in the short and in the long term between patients that received N/S or L/R.

The KDIGO guidelines for AKI conclude that whether the use of buffered solutions results in better outcomes is uncertain [20]. There are data both from experimental and human AKI settings that point out that administration of crystalloids in the form of N/S results in hyperchloremia [21–23]. In our study, patients that were treated with N/S showed an increase in plasma Cl^- compared to patients who received L/R. Moreover, mean plasma Cl^- on discharge was above normal values for both groups, which emphasizes that the choice of fluids can make a difference during treatment. However, despite these differences in plasma Cl^- , this did not seem to alter kidney function improvement in short and long term.

Infusion of L/R is accompanied by a significant improvement of acid-base profile and HCO_3^- concentration in comparison to N/S, especially in patients with diabetic ketoacidosis [24,25]. Even in an experimental pig model, N/S infusion caused a pH reduction while L/R infusion

maintained arterial pH unchanged [26]. In our study, that included patients with limited capacity of HCO_3^- regeneration and net acid excretion, treatment with L/R showed a constant trend of increasing pH towards normal values. On the contrary, N/S infusion resulted in decreasing pH values during the first 2 days with subsequent improvement afterwards. More importantly, pH improvement between admission and discharge was higher in patients that received L/R.

Concerning the adverse effects of treatment, no case of severe hyperkalemia occurred in any of the patients. This is in accordance with other studies, both in patients with diabetic ketoacidosis, where a potassium deficit prevails and L/R administration is associated with less hypokalemia events [24], and in critically ill patients [27–29]. This finding is even more important in our patients, as due to both established CKD and AKI they have limited kidney potassium excretion capacity. Moreover, none of the patients showed signs of volume overload. Finally, all patients responded well to treatment with no need for dialysis initiation as a result of treatment failure.

To our knowledge, this is the first study of a restrictive approach to the use of chloride rich fluids in a homogeneous highly selected population of patients with pre-renal AKI and pre-established CKD. A strength of our study is the adherence to the assigned crystalloid group throughout the treatment period. Moreover, the biochemical measurements were extended throughout the intervention period and for many patients for 30 days after discharge. Use of an unblinded, pragmatic design could produce a bias in patients selection in a specific treatment arm, however baseline characteristics did not show any significant differences between groups. Limitations of the study include its single center setting and the small sample size. The study aimed at a specific patient population with CKD stage-III or more with pre-specified strict AKI criteria.

In conclusion, treatment of patients with pre-renal AKI and pre-established CKD with L/R seems to be at least of equal value to N/S. L/R infusion is as efficient as N/S in improving kidney function while it has the advantage of preventing hyperchloremic acidosis.

Introducere: Serul fiziologic (N/S) și Soluția Ringer Lactat (L/R) sunt administrate zilnic. Totuși, N/S crește riscul încărcării cu sodiu și al dezvoltării acidozei metabolice hipercloremice. Pe de altă parte, L/R are un conținut mai mic de sodiu, mai puțin clor și mai mult acid lactic. Scopul studiului a fost de a evalua eficiența L/R versus N/S la pacienții cu insuficiență acută prerenală (AKI) și cu boli renale cronice (CKD).

Metode: A fost realizat un studiu prospectiv unde au fost incluși pacienți cu AKI prerenală sau CKD stadiile III-V ce nu necesitau dializă. Au fost excluși pacienți cu alte forme AKI, hipervolemie sau hiperkalemie. Pacienții au primit N/S sau L/R intravenos la o doză de 20 mL/kgc/zi. Am studiat funcția renală la externare și 30 de zile postexternare, durata spitalizării, echilibrul acido-bazic, precum și nevoia de dializă.

Rezultate: Am studiat 38 de pacienți, 20 au fost tratați cu N/S. Funcția renală a fost similară între cele două grupuri. Durata spitalizării a fost similară. Anion-gap dintre momentul internării și externării a fost mai bun la pacienții cu L/R comparativ cu pacienții cu N/S, iar creșterea pH-ului (ΔpH) a fost ușor mai mare la pacienții ce au primit L/R. Niciun pacient nu a necesitat dializă.

Concluzii: Administrarea L/R sau N/S la pacienții cu AKI prerenală sau CKD nu a arătat diferențe asupra funcției renale, dar L/R a arătat un profil mai bun în privința echilibrului acido-bazic.

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