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Original Article

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Comparison of Sodium Bicarbonate Capsules and Gastro-Resistant Sodium Bicarbonate Tablets in Patients with Stage 4 Chronic Kidney Disease

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ABSTRACT

Objective: In this study, we aimed to compare stage 4 chronic kidney disease patients who received sodium bicarbonate treatment in the form of 500 mg capsules and 1000 mg gastro-resistant tablets.
Methods: All patients with stage 4 chronic kidney disease presenting to the nephrology clinic between August 2020 and November 2020 were evaluated retrospectively. The patients were divided into 2 groups: sodium bicarbonate group and gastro-resistant sodium bicarbonate group. Groups were compared in terms of serum bicarbonate and side effects during follow-up.
Results: A total of 43 stage 4 chronic kidney disease patients were included in this study. The bicarbonate change in both groups was statistically significant after the first week ($P < .001$). In the gastro-resistant sodium bicarbonate group bicarbonate level was significantly higher than the sodium bicarbonate group in the first week ($P < .001$).
Conclusions: Gastro-resistant sodium bicarbonate seems to normalize serum sodium bicarbonate earlier than sodium bicarbonate.
Keywords: Bicarbonates, chronic kidney disease, metabolic acidosis

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INTRODUCTION

The average daily acid production in adults is around 1 mEq/kg, although the daily acid production in children reaches 2-3 mEq/kg. Normally, the acid-base balance is maintained by the kidney excretion of the daily acid load. Metabolic acidosis may occur as a result of increased non-volatile acid production, increased bicarbonate loss, and decreased kidney acid excretion. Metabolic acidosis is often associated with chronic kidney disease (CKD) and is one of the most important complications of CKD.[2] It generally seems in advanced CKD, particularly when glomerular filtration rate (GFR) decreases under 30 mL/min.[3]

Metabolic acidosis in CKD may cause osteopenia and osteoporosis,[4] increased muscle catabolism,[5] exacerbation of secondary hyperparathyroidism,[6] systemic inflammation,[7] and is also associated with increased mortality[8] and accelerated CKD progression.[9-11] Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends maintaining serum bicarbonate levels within the normal reference range (23-29 mEq/lt, mEq/L) and similarly Kidney Disease Outcomes Quality Initiative guideline recommends initiating base replacement when bicarbonate level is < 22 mEq/lt.[12, 13]

It is reported in the literature that 2 forms of drugs are used for oral sodium bicarbonate support: oral solutions and gelatin capsules.[14] In studies conducted with cyclists, it has been shown that solution and capsule forms provide bicarbonate release with similar strength.[15] Until recently, only 500 mg capsule forms of oral sodium bicarbonate were available in our country. Gastro-resistant

tablets containing 1000 mg sodium bicarbonate have been available for prescription in our country a short while ago.

In this study, we aimed to compare the therapy outcomes of stage 4 CKD patients who received sodium bicarbonate in the form of 500 mg capsules and 1000 mg gastro-resistant tablets.

METHODS

Participants

The files of all patients who presented to the nephrology outpatient clinic between August 1, 2020, and November 1, 2020, were retrospectively scanned. Patients with stage 4 CKD (estimated glomerular filtration rate (eGFR) = 15-29 mL/min/1.73 m^2) and newly started bicarbonate therapy because of metabolic acidosis were included in the study. Patients who were already under sodium bicarbonate treatment were not included. Patients under 18 years of age, with acute kidney injury, hypokalemia, pregnancy, uncontrolled hypertension, hypervolemia, and urgent need for dialysis were excluded from the study. Patients who did not have sufficient laboratory data for the study were also excluded. Patients who received sodium bicarbonate in 500 mg capsules were named as sodium bicarbonate (SB) group, and patients who received sodium bicarbonate in 1000 mg gastro-resistant tablets were named as gastro-resistant sodium bicarbonate (GRSB) group. Figure 1 shows the patients included in the study, patient groups, and study design.

Laboratory Measurements

Demographical and clinical data were obtained from electronic files of patients. Bicarbonate levels were evaluated using venous blood gas samples for all patients. Sodium bicarbonate starting day was considered as day 0. Bicarbonate levels were recorded in the first week, first month, and third month after the start day. Venous blood gas samples of all patients were studied with the Siemens RapidLab 1265 (Germany, 2008) device.

Statistical Analysis

Categorical variables were presented as numbers and percentages. Chi-square test was used for comparing categorical variables between groups. Conformity of continuous variables to normal distribution was checked with visual histograms and Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation (SD). Continuous variables without normal distribution were presented as the median and interquartile range (IQR). Mann–Whitney *U*-test or independent samples *t*-test was used for continuous variable comparisons between groups according to the presence of normal distribution. Friedman test was used for in-group comparisons. All presented *P* values are two-sided and $P < .05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences 26.0 (IBM, SPSS Inc., Chicago, IL, USA) package program.

RESULTS

A total of 43 stage 4 CKD patients were included in this study. Twenty-three of the patients (53.5%) were in the GRSB group and 20 patients (46.5%) were in the SB group. Of the 43 patients in the study group, 22 (51.2%) were women. The median age of the study group was 56 years (IQR 25-75 = 52-62 years). Thirty-four (79.1%) of the patients had a diagnosis of hypertension and 30 patients (69.8%) had diabetes mellitus. Of the 43 patients, 28 (65.1%) had CKD due to diabetic nephropathy, 9 (20.9%) due to hypertension, 3 (7%) secondary to chronic glomerulonephritis, 2 (4.7%) due to obstructive

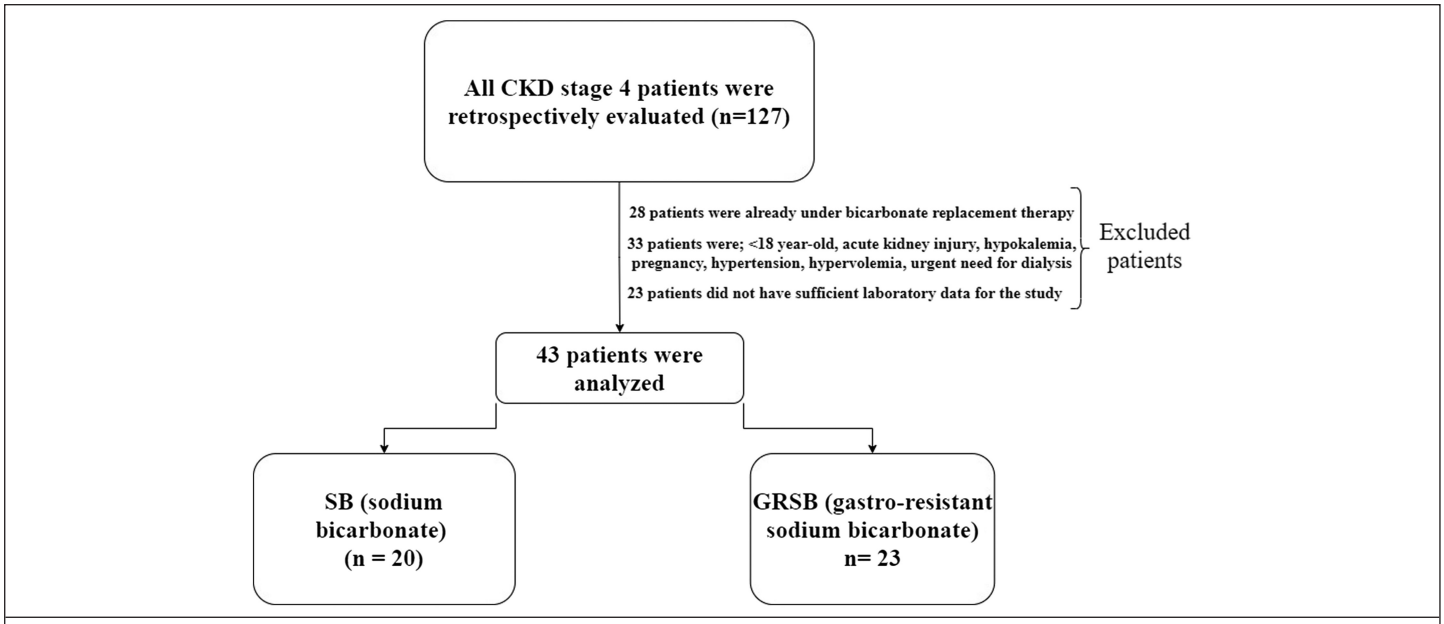

Figure 1. Study design.

nephropathy, and 1 (2.3%) due to polycystic kidney disease. Groups were similar in terms of CKD etiology and demographical characteristics. Table 1 shows the general characteristics of the groups.

The patients were similar in terms of laboratory features on day 0. Table 2 shows the comparison of the laboratory parameters of the patients before they started taking bicarbonate replacement.

During the study, the patients in both groups did not need a drug dose change. The bicarbonate change in both groups was statistically significant after the first week (P <.001). Table 3 shows the bicarbonate levels of groups during the study period.

Although all the subjects in both groups reached the target bicarbonate range, the bicarbonate level in the GRSB group was significantly higher than the SB group in the first week (P < .001) (Figure 2).

eGFR was 17.35 ± 1.9 mL/min/1.73 m^2, 17.30 ± 1.93 mL/min/1.73 m^2, and 17.31 ± 1.97 mL/min/1.73 m^2 in GRSB group on the seventh day, first month, and third month, respectively. In SB group, eGFR was 18.20 ± 2.4 mL/min/1.73 m^2, 18.25 ± 2.36 mL/min/1.73 m^2, and 18.19 ± 2.45 mL/min/1.73 m^2 on seventh day, first month, and third month, respectively. eGFR values of both groups were similar on seventh day, first month, and third month with baseline values (P = .205, P = .134, and P = .137, respectively). Gastrointestinal side effects (nausea and vomiting) were mild in both groups. No patient who experienced a serious side effect that required the discontinuation of drugs in both groups. They were reported in 5 patients (21.7%) in the GRSB group and 9 patients (45%) in the SB group. Groups were similar in terms of gastrointestinal side effects (P = .191).

Table 1. Comparison of the Groups in Terms of General Characteristics

Characteristic	SB (n = 20)	GRSB (n = 23)	P
Age (years/IQR 25-75)	58/49.5-62	55/52-62	.654*
Female gender (n/%)	9/45	13/56.5	.547**
DM (n/%)	14/70	16/69.6	.975***
HT (n/%)	16/80	18/78.3	.889***
CKD etiology (n/%)			
DM	13/65	15/65.2	.685**
HT	3/15	6/26.1	
GN	2/10	1/4.3	
ON	1/5	1/4.3	
PKD	1/5	0	
Dose (mg/IQR 25-75)	3000/2000-3000	3000/2000-3000	.701*
Weight (kg/IQR 25-75)	72.35/61.7-76.6	72.2/63.5-75.6	.808*
Systolic BP (mmHg/IQR 25-75)	130/126.5-137.5	129/127-141	.509*
Diastolic BP (mmHg/IQR 25-75)	81/79.25-86.75	84/79-93	.471*

*Mann–Whitney U test, **Chi-square test, ***Fisher's exact test.
DM, diabetes mellitus; HT, hypertension; GN, glomerulonephritis; ON, obstructive nephropathy; PKD, polycystic kidney disease; BP, blood pressure.

Table 2. Baseline Laboratory Comparisons of the Groups

Parameters	SB (n = 20)	GRSB (n = 23)	P
Urea (mg/dL)	98.8 ± 9.8	100.04 ± 12.1	.345*
Creatinin (mg/dL)	4.51 ± 0.54	4.8 ± 0.68	.137*
eGFR (mL/min/1.73 m^2)	18.22 ± 2.4	17.33 ± 0.16	.197*
Sodium (mEq/lt)	139.6 ± 1.72	139.52 ± 2.4	.906*
Potassium (mEq/lt)	4.6 ± 0.4	4.58 ± 0.3	.878*
Phosphorus (mg/dL)	4.83 ± 0.4	4.96 ± 0.3	.216*
Calcium (mg/dL)	8.73 ± 0.1	8.81 ± 0.1	.09*
pH	7.28 ± 0.02	7.28 ± 0.02	.634*
HCO_3 (mEq/lt)	17.49 ± 1.2	17.4 ± 1.58	.836*
Albümin (gr/dL)	4.1 ± 0.2	4.1 ± 0.17	.572*
PTH (pg/mL)	122.65 ± 13.6	122.3 ± 12.5	.932*

*Independent samples t-test.
PTH, parathyroid hormone.

Table 3. In-Group Bicarbonate Comparisons During Study Period

	HCO_3 (mg/dL)	Chi-square	P
SB (n = 20)			
HCO_3-Day 0	17.49 ± 1.2	43.89	**<.001***
HCO_3-first week	24.03 ± 0.36		
HCO_3-first month	24.77 ± 0.95		
HCO_3-third month	24.7 ± 0.98		
GRSB (n = 23)			
HCO_3-Day 0	17.4 ± 1.58	43.47	**<.001***
HCO_3-first week	25.2 ± 1.14		
HCO_3-first month	25.2 ± 1.26		
HCO_3-third month	25.38 ± 1.2		

*Friedman test.
A P-value less than 0.05 was considered statistically significant and is shown in bold in the Table.

DISCUSSION

For cells to function normally, intracellular and extracellular power of hydrogen (pH) must be kept within a certain range. Buffer systems and organs such as kidneys, lungs, and bone

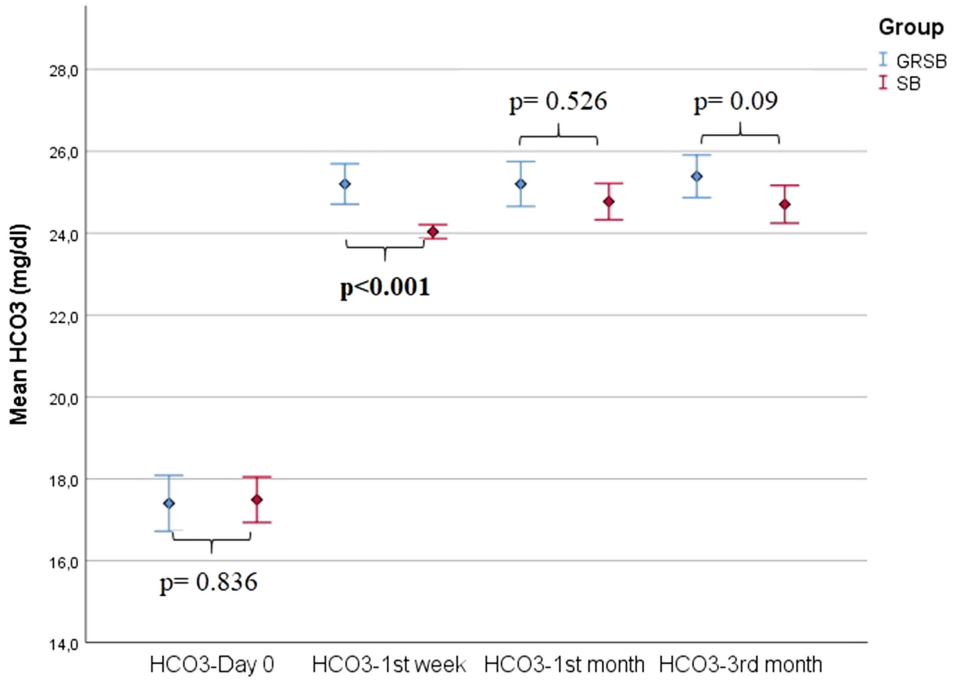

Figure 2. Comparison of HCO_3 levels by time between groups.

have roles in blood pH regulation. The main target of the mechanisms that provide acid-base balance is the elimination of acidic substances that occur as a result of cell metabolism.

In kidney failure inability to evacuate the H^+ charge and increase in kidney HCO_3^- loss leads to metabolic acidosis. Metabolic acidosis is a risk factor for the progression of kidney disease. Chronic Kidney Insufficiency Cohort Study that included 3939 participants with CKD showed that serum bicarbonate levels are associated with kidney outcomes.[16] Studies show that the sodium bicarbonate treatment slows down the process in CKD.[17] A retrospective study of 6380 patients in the Multi-Ethnic Study of Atherosclerosis showed that patients with bicarbonate concentration < 21 mmol/L are 35% more likely to have a decrease in kidney function than those with 23-24 mmol/L.[18]

The Clinical Practice Guideline for the Assessment and Management of Chronic Kidney Disease (KDIGO-2012) recommends that patients with CKD should receive oral bicarbonate supplements if their serum bicarbonate concentrations are below 22 mmol/L, unless contraindicated.[12]

A 500 mg oral sodium bicarbonate capsule form contains hydrated soybean oil, propylene glycol, mannitol, and sorbitol as excipients. It should not be given to people with peanut allergies due to soybean oil. Propylene glycol can cause alcohol-like symptoms. Mannitol and sorbitol can create laxative effects. Regardless of the etiology, it is indicated for the treatment and prophylaxis of metabolic acidosis. The recommended dosage is 6-9 capsules per day. Capsules dissolve in the intestinal tract after oral intake and are almost completely absorbed, with bioavailability similar to sodium bicarbonate infusion. After absorption, it diffuses into intracellular and extracellular space in the body and decomposes into sodium and bicarbonate ions in water. Plasma electrolytes should be monitored due to the sodium it contains. HCO_3^- increases the plasma alkali reserve. When its value in the blood exceeds 28 mEq, it is excreted in the urine.

Gastro-resistant sodium bicarbonate is a bicarbonate replacement drug that has been recently introduced in our country. Each tablet contains 1000 mg sodium bicarbonate. Due to its gastro-resistant feature, it is absorbed from the intestinal system through the stomach unchanged. Gastro-resistant sodium bicarbonate group contains sodium starch glycolate and lactose monohydrate as additional excipients. Those with lactase deficiency glucose-galactose malabsorption should use it carefully. In addition, it has a formulation obtained by adding cellulose to the structure of sodium bicarbonate. Cellulose is a polysaccharide that is found in the plant cell wall and makes the molecule it is added resistant to gastric acidity.[19] Gastro-resistant tablets may remain stable in the acidity of the stomach and degrade in more alkaline pH values. Therefore, symptoms such as nausea and vomiting may be reduced with cellulose-coated sodium bicarbonate tablets.[19] It may be theoretically predicted that cellulose-coated molecules may have less gastrointestinal system side effects than molecules without cellulose. In our study, the SB group had 2-fold more gastrointestinal side effects than the GRSB group, but this was not statistically significant. Studies with more patients may provide more precise information on this issue.

Treatment of metabolic acidosis in CKD slows down the progression of CKD and has a direct impact on the patient's quality of life.[17, 20-22] However, it has been shown that high serum bicarbonate levels in the normal reference range may prevent CKD progression in elderly patients with CKD.[23] Recently, low serum bicarbonate within the normal range is found to be associated with worse kidney function and further eGFR decline in patients with polycystic kidney disease.[24] In our study, serum bicarbonate levels of both groups were significantly increased but in the comparisons between groups, it was found that the bicarbonate level in the first week was significantly higher in the GRSB group. We think that providing the same amount of sodium bicarbonate support with a smaller number of drugs may play a role in drug compliance.

As it is well known, nephrology patients have the highest comorbidity, the highest number of drugs prescribed, and the highest mortality rates, and they are the patients in whom polypharmacy is the most problematic.[25] A multi-center study conducted in 2020 showed that elderly patients who have CKD, in particular, have an increased risk of potential drug-related problems.[26] In order to avoid polypharmacy and increase drug compliance, it may be a rational way to give the same dose with a less number of tablets.[25, 27–29] In our study, groups were similar in terms of median sodium bicarbonate dose, and bicarbonate levels return to normal in both groups from the first week, but the GRSB group had significantly higher bicarbonate levels in the first week. This suggests that patients in the GRSB group were protected earlier from the harmful effects of metabolic acidosis such as osteopenia, osteoporosis, increased muscle catabolism, accelerated CKD progression, and even increased mortality.

Both drug formulations have 50 000 mg sodium bicarbonate per pillbox (SB; 500 mg per pill and 100 pills, GRSB; 1000 mg per pill and 50 pills). According to 2021 retail drug prices, GRSB appears to be cheaper than SB. Our findings suggest that GRSB normalizes serum bicarbonate levels earlier and at less cost than SB. It has been shown in a study that up to 40% of total health expenditures are spent on drugs.[30] In the whole world, it is known that about 1 in 10 adults has kidney disease at various stages. It is a very important burden for the health expenditure system, so cost-effectiveness in the management of chronic diseases should not be overlooked. GRSB appears to be more cost-effective than SB.

CONCLUSION

In conclusion, this is the first study comparing two different forms of oral sodium bicarbonate in patients with stage 4 CKD. Gastro-resistant sodium bicarbonate group seems to normalize serum sodium bicarbonate earlier than SB. The retrospective design, small number of patients, and the absence of patient–drug compliance data may be considered as the limitations of our study. Although groups were similar statistically, mild gastrointestinal symptoms were less common in the GRSB group. More comprehensive and prospective studies may guide the efficacy and side effects of different forms of sodium bicarbonates in patients with CKD.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Afyonkarahisar Health Sciences University (Date: July 03, 2020, Decision No: 2020\317).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.DK., S.K., O.T., J.A., S.U.; Design – E.DK., S.K., O.T., J.A., S.U.; Supervision – E.DK., S.K., O.T., S.U.; Materials – E.DK., S.K., O.T., J.A.; Data Collection and/or Processing – E.DK., S.K., O.T., S.U.; Analysis and/or Interpretation – S.K., O.T., S.U.; Literature Review – E.DK., S.K., O.T., J.A., S.U.; Writing – E.DK., S.K., O.T., J.A.; Critical Review – S.K., O.T., S.U.

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