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RESEARCH LETTER

Randomized Trial on the Efficacy and Safety of Standard Versus Higher Bicarbonate Supplementation in CKD of Unknown Etiology

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Received 2 November 2023; revised 24 January 2024; accepted 5 February 2024; published online 12 February 2024

Kidney Int Rep (2024) **9,** 1504–1507; https://doi.org/10.1016/j.ekir.2024.02.008
KEYWORDS: alkali therapy; metabolic acidosis; sodium bicarbonate; tubulointerstitial diseases

INTRODUCTION

A bicarbonate level of less than 22 mEq/l is associated with an increased risk for chronic kidney disease (CKD) progression, reduced bone mineral density, loss of muscle mass, and all-cause mortality.[1] Many previous studies have shown that bicarbonate supplementation in the dose range of 0.3 to 0.5 mEq/kg body weight (KBW) is safely tolerated, raising the feasibility of escalating the doses to 0.8 mEq/KBW in subsequent clinical trials.[2] Observational data suggests a survival benefit when bicarbonate levels are the in 26 to 28 mEq/l range.[1] Most of the early trials focused on correction up to 22 to 25 mEq/l. A few recent randomized controlled trials attempted correcting bicarbonate levels up to 26 to 28 mEq/l; however, the results on kidney protection are nonconclusive, with concerns of cardiac failure, worsening of hypertension, and effects on proteinuria.[2] Our center is located in a CKD of unidentified etiology (CKDu) hotspot, and previous studies have reported metabolic acidosis in 85% of the CKD population.[3,4] CKDu is often underrepresented in alkali supplementation studies aiming to prevent the progression of CKD. The present study is a feasibility study on higher bicarbonate correction (HC) versus standard bicarbonate correction on nonproteinuric CKDu.

RESULTS

One hundred twenty-eight patients were randomized, and all completed the study (Supplementary Table S1). Most (95.3%; $n = 122$) were from rural areas and engaged in manual labor such as farming and construction. The baseline clinical characteristics at recruitment are given in Table 1. The sliding scale used for initial bicarbonate prescriptions are given in Supplementary Table S1.

Bicarbonate Levels, Drug Adherence, Tolerability, and Adverse Effects

The changes in venous bicarbonate over 3 months are given in Supplementary Figure S2. The weight-based dosing was 0.44 mEq/KBW (95% confidence interval: 0.37–0.50) in the SC arm and 0.56 mEq/ KBW (95% confidence interval: 0.52–0.6) in the HC arm ($P < 0.006$). The outcomes are presented in Table 2; other biochemical parameters are presented in Supplementary Table S2 . In the SC arm, 75% ($n = 50$) attained the target venous bicarbonate levels, whereas only 25% ($n = 16$) reached the target level in the HC arm. Those who failed to achieve target levels had considerably lower venous bicarbonate levels at entry (17.5 mEq/l [95% confidence interval: 17.2–18.4] vs. 18.4 mEq/L [95% confidence interval: 18.4–19.1]; $P = 0.012$) and a higher pill burden (3 g [interquartile range: 2–3] vs. 1.5 g [interquartile range:1.5–3]; $P < 0.001$], compared to those who attained target levels. The maximum tolerated dose in the HC arm was 6 g (12 tablets). Despite the increased sodium load in the HC arm, there were no differences in blood pressure or

Table 1. Baseline characteristics of the high dose (HC) and standard dose (SC) arms

Parameter	Higher correction (HC) arm $n = 64$	Standard correction (SC) arm $n = 64$	*P*- value
Age (yr)[a]	52.5 (49.5, 55.5)	53.1(50.4, 55.9)	0.742
Sex, *n* (%)	50 (78)	48 (75)	0.676
Weight (kg)[a]	58.6 (56, 61.3)	58.6 (56, 61.1)	0.99
Body mass index (kg/m^2)[a]	22.8 (21.8, 23.9)	22.6 (21.6, 23.6)	0.757
Smoking, *n* (%)	4 (6.3)	1 (1.6)	0.365
CKD of unidentified etiology, *n* (%)	59 (92)	59 (92)	0.333
CKD stage 3a, *n* (%)	15 (23)	9 (14)	
CKD stage 4, *n* (%)	39 (61)	35 (55)	0.080
CKD stage 5 ND, *n* (%)	10 (16)	20 (31)	
Systemic hypertension, *n* (%)	42 (66)	39 (61)	0.582
Cardiac diseases, *n* (%)	6 (9.4)	2 (3.2)	0.273
Systolic blood pressure (mm Hg)[a]	125 (120, 129)	129 (125, 133)	0.079
Diastolic blood pressure (mm Hg)[a]	76 (74, 78)	77 (74, 80)	0.158
Calcium channel blockers, *n* (%)	38 (59)	30 (45)	0.156
Renin angiotensin aldosterone blockers, *n* (%)	9.4 (6)	4 (6.3)	0.510
Beta blockers, *n* (%)	8 (13)	15 (23)	0.107
Diuretics, *n* (%)	25 (39)	28 (44)	0.590
Phosphate binders, *n* (%)	9 (14)	13 (20)	0.370
Urea (mg/dl)[a]	69.8 (64.1, 75.5)	74 (65, 83)	0.448
Creatinine (mg/dl)[b]	2.88 (2.36, 3.73)	3.04 (2.24, 4.16)	0.514
eGFR (ml/min per 1.73 m^2)[a]	24.4 (22.1, 26.8)	23.1 (20.6, 25.6)	0.447
Uric acid(g/d)[a]	8.1 (7.57, 8.56)	7.91 (7.36, 8.45)	0.671
Sodium (mEq/l)[a]	136 (135, 137)	137 (135, 137)	0.786
Potassium (mEq/l)[a]	4.32 (4.16, 4.49)	4.42 (4.27, 4.58)	0.403
Chloride (mEq/l)[a]	101 (100, 102)	102 (101, 103)	0.136
Parathyroid hormone (pg/ml)[b]	136 (100, 190)	149 (63, 256)	0.707
Calcium (mg/dl)[a]	9.31 (9.17, 9.47)	9.38 (9.22, 9.48)	0.774
Phosphorus(mg/dl)[a]	3.91 (3.70, 4.13)	3.88 (3.66, 4.10)	0.821
Alkaline Phosphatase (IU/l)[b]	108 (82, 142)	99 (82, 131)	0.353
Fasting blood sugar (mg/dl)[a]	96 (92, 99)	93 (89, 97)	0.285
Cholesterol(g/dl)[b]	157 (141, 200)	162 (138, 192)	0.603
Albumin (g/dl)[a]	4.2 (4.1, 4.3)	4.2 (4.1, 4.3)	0.138
pH[a]	7.31 (7.28, 7.33)	7.30 (7.29, 7.31)	0.155
pCO2(mm Hg)[a]	39.4 (38.2, 40.6)	38 (37, 40)	0.258
Bicarbonate (mEq/l)[a]	18.2 (17.5, 18.8)	17.9 (17.2, 18.5)	0.106
Base excess[b]	−6.4 (−8, −4.6)	−7 (−8.4, −5)	0.410
Urine Sodium (mEq/l)[b]	84 (64, 137)	87 (65,137)	0.907
Urine Potassium (mEq/l)[b]	23 (14, 35)	26 (19, 38)	0.472
Urine Chloride (mEq/l)[b]	86 (63, 136)	99 (62, 147)	0.662

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]mean with 95% confidence interval.
[b]median with IQR.

weight compared to the SC arm (Supplementary Table S2). The urinary sodium excretion increased in both arms compared to baseline (Supplementary Table S2). On regression analysis, the use of calcium carbonate as phosphorus binder had no effect on final bicarbonate levels ($P = 0.166$). No serious adverse effects needing discontinuation were noticed. The kidney function at exit were comparable; and there was a significant increase in albuminuria in the HC arm (Supplementary Table S3)

DISCUSSION

Recent guidelines incorporate alkali therapy in CKD when bicarbonate levels are <22 mEq/l. The optimum upper range of bicarbonate supplementation in CKD remains elusive. Observational data from the CRIC cohort and AASK reported that venous bicarbonate levels in the 25 to 30 mEq/l range are associated with improved patient and kidney survival.[5,6] Despite observational data reporting beneficial effects with bicarbonate levels >30 mEq/l, randomized controlled trials seldom report attaining such high levels. In the present study, even though we targeted a bicarbonate level of 26 to 28 mEq in the HC arm, we could obtain only levels closer to 25 mEq/l, with only 25% of patients reaching the prespecified venous bicarbonate targets. The venous bicarbonate levels in the early randomized trials targeted 22 to 24 mEq/l range. Venous bicarbonate levels closer to 28 mEq/l appear challenging to achieve

Table 2. Bicarbonate levels, drug adherence, tolerability, and adverse effects

Parameter, *n* (%)	Higher correction (HC) arm, *n* = 64	Standard correction (SC) arm, *n* = 64	*P*-value
Venous bicarbonate (mEq/l)[a]	24.7 (24.1, 25.4)	22.7 (22.1, 23. 3)	0.001
Change in bicarbonate from baseline (mEq/l)[a]	6.0 (5.3, 6.6)	4.7 (4.1, 5.2)	0.003
Change in pH from baseline	0.05 (0.04, 0.07)	0.06 (0.04, 0.07)	0.228
Bicarbonate dose (mg)[b]	3000 (2000, 3000)	2000 (1500, 3000)	<0.001
Target bicarbonate levels achieved, *n* (%)	16 (25%)	50 (75%)	
Overall adverse effects, *n* (%)	38 (60)	29 (45)	0.111
Serious adverse effects /drug withdrawal, *n* (%)	0	0	-
Drug compliance, *n* (%)	58 (91)	59 (92)	0.752
Concerns of pill burden, *n* (%)[d]	37 (58%)	18 (28.1)	0.001
Worsening hypertension, *n* (%)	22 (35)	14 (22)	0.116
Increase in antihypertensives, *n* (%)	05 (7.8)	03 (4.7)	0.370
Increase in diuretics, *n* (%)	10 (15)	08 (12.5)	0.611
Gastrointestinal disturbances[e], *n* (%)	11 (17)	10 (16)	0.811
Edema, *n* (%)	4 (6)	2 (3)	0.403
Serum Potassium <3 mEq/l[c]	1 (2)	0	1.000
Serum calcium <8.8 mg/dl[c]	10 (16)	14 (22)	0.365
Hospitalizations, *n* (%)	0	0	-
Withdrawal criteria *n* (%)	-	-	-

[a]mean with 95% Confidence Interval.
[b]median with interquartile range.
[c]documented on exit visit, none had neuromuscular symptoms or electrocardiogram changes.
[d]based on patient feedback of not being comfortable with the total number of pills prescribed, and/or not approving any further increase.
[e]any 1 or more of self-reported symptoms - new onset loss of appetite, nausea, vomiting, unpleasant taste in mouth, bloating/abdominal distension, or feeling of fullness.

in a trial setting. The recent Base–PILOT and UBI trials were designed for a higher bicarbonate correction of up to 28 mEq/l. Despite administering 0.8 to 1.1 mEq/KBW of bicarbonate, the target bicarbonate levels achieved were only about 25 to 26 mEq/l.[2,7] The baseline bicarbonate levels in these trials were 25 and 21.5 mEq/l, considerably higher than the bicarbonate levels in the present study. We believe the low baseline bicarbonate levels might be a potential contributory factor in the present study's failure in reaching prespecified targets. None of the studies targeting higher bicarbonate correction has examined changes in urine pH or venous bicarbonate excretion. Once the upper venous bicarbonate levels are reached, whether diseased kidneys start to excrete bicarbonate remains unknown. In the UBI study, venous bicarbonate levels of 22 mEq/L were attained at a dose of 0.28 mEq/KBW in the control arm. In contrast, the high-dose arm could attain only a bicarbonate level of 26 mEq/L despite receiving an almost 4-fold requirement of bicarbonate (mean 1.1 mEq/KBW).[7]

Another significant limitation in attaining the target bicarbonate level were the open-label nature of the present trial and the use of 500 mg tablets. Despite having an overall compliance of >90%, about two-thirds of patients in the HC arm were concerned about pill burden, which was a significant roadblock in dose escalation. It might be prudent to consider 1000 mg pills in future trials. In the Base PILOT and UBI trials, the reported attrition in the HD arm was 9% and 14% at 28 weeks and 3 years, respectively.[2,7] Pill burden is a major concern in ensuring compliance with long-term treatment outside the trial setting.

The overall adverse effect profile was comparable. The increased sodium load was compensated by increased sodium excretion, as reported by many previous trials.[2,7,8] However, we found a tendency for an increase in urine albumin-to-creatinine ratio (UACR) in both arms, with a higher magnitude in the HC arm. The previous 2 trials with 1.0 mEq/KBW of citrate/bicarbonate, targeting to correct bicarbonate to 22 and 24 mEq/L, did not report increased UACR.[S1,S2] The Base Pilot study reported a dose-dependent increase in UACR—12% in the low-dose arm and 30% in the high-dose arm.[2] This raises the question of whether bicarbonate has an upper threshold beyond which sustained increases in UACR occur. Recent data suggest that bicarbonate supplementation can modulate hemodynamic parameters by changing the endothelial reactivity and afferent arteriolar tone.[S3,S4] Including UACR and glomerular filtration rate as the coprimary end points for future trials might be prudent.

As expected, we did not find any differences in estimated glomerular filtration rate. The duration was kept at 3 months, primarily to assess the feasibility of a future trial with a longer duration. The nephroprotective effects of bicarbonate might take more time to become evident. It should also be noted that only a quarter of patients were able to raise their bicarbonate levels to 26 to 28 mEq/L in the HC arm; possible contributory factors might be the open label nature of the trial, use of 500 mg tablets and recruitment of patients with severe acidosis (<18 mEq/L of bicarbonate).

It might be prudent undertake a pilot trial including a placebo arm, use pills of higher strength, and limiting recruitment to patients with a moderate degree of acidosis, before embarking a larger trial.

To our understanding, this is the first trial of alkali supplementation in patients with CKDu. The strengths of the trial include recruiting patients with prevalent CKDu with stable kidney function. Compliance was assessed by pill counts, and all outcome assessments were made by people unaware of treatment allocation. All the laboratory measurements were subjected to rigorous internal and external standardizations. We have not quantified the dietary acid load in the population; previous studies from the same geographic area had documented low dietary protein intake despite a mixed diet consumption.[4]

CONCLUSION

In patients with CKDu, 3-month bicarbonate supplementation targeting venous bicarbonate levels of 26 to 28 mEq/L was well-tolerated. No significant safety concerns were observed during the study, barring the pill burden, raising the possibility of considering a higher target bicarbonate correction in future trials. There was a tendency of rising UACR in both arms; more evident in the HC arm. More extensive trials, with longer follow-up durations, are needed for the safety and efficacy of bicarbonate supplementation, targeting limits closer to 28 mEq/L.

DISCLOSURE

All the authors declared no conflicting interests.

ACKNOWLEDGMENTS

This study was funded by the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Study Design and Methods.

Supplementary References.

Figure S1. Consort diagram.

Figure S2. Changes in bicarbonate levels over study period.

Table S1. Sliding scale used for initial bicarbonate dosing.

Table S2. Clinical and biochemical characteristics of the HC and SC intervention groups at exit.

Table S3. Renal function at exit.

CONSORT Check list.

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