Safety & Effect of Alkali Therapy on Vascular Function in Kidney Transplant Recipients: A Pilot Randomized Cross-Over Study

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Background

- Cardiovascular disease is the leading cause of death in kidney transplant recipients (KTRs).[1,2]
- KTRs with lower serum bicarbonate levels have an increased risk of graft loss, cardiovascular events and mortality.[3-6]
- Bicarbonate administration was previously shown to slow disease progression and improve vascular function in patients with CKD.[7]
- We tested the hypothesis that sodium bicarbonate therapy was safe and feasible in KTRs and would improve vascular endothelial function.

Methods

Study Participants

- 20 adult KTRs that were ≥ 1 year from transplant with baseline eGFR ≥ 45 mL/min/1.73m^2 and serum bicarbonate of 20-26 mEq/L.
- All patients had to be on a stable immunosuppressive and anti-hypertensive regimen for at least 1 month.
- Exclusion Criteria:
  - BMI ≥ 40 kg/m^2
  - Uncontrolled HTN
  - Heart Failure (NYHA Class 3-4 or known EF ≤ 30%)
  - Significant comorbidities resulting in life expectancy <1 year
  - Serum potassium < 3.3 or > 5.5
  - Use of supplemental oxygen

Study Design

- 18-week, randomized, double blind, placebo-controlled crossover safety and feasibility pilot study.
- Each treatment period was 8 weeks in duration with a 2-week washout period in between.
- Each patient served as his or her own control.

Primary Outcome

- Change in brachial artery flow-mediated dilation (FMD), measured by high-resolution ultrasonography.

Sodium Bicarbonate Dosing

- Dose = 0.5 mEq/kg of lean body weight/day for entire 8 weeks.
- Each sodium bicarbonate tablet contained 7.7 mEq bicarbonate and 178 mg of sodium.
- Study drugs were identical in size, color, shape and taste.
- Matching placebo pill contained cornstarch.

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Results

Figure 1. Percent FMD at baseline and 8 weeks after sodium bicarbonate administration

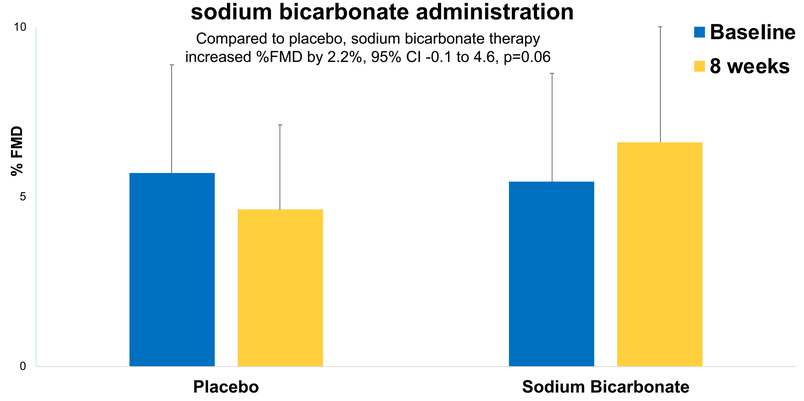

Table 1. Baseline Characteristics of Study Population

Characteristic	
Age (years)	52 ± 17
Gender N(%)	
Male	16 (80.0)
Female	4 (20.0)
Race N (%)	
Non-Hispanic White	15 (75.0)
Non-Hispanic Black	0 (0.0)
American Indian	1 (5.0)
Asian	1 (5.0)
Multiple races	1 (5.0)
Unknown/not provided	2 (10.0)
Etiology of Kidney Disease N (%)	
Diabetes	3 (15.0)
Hypertension	4 (20.0)
Glomerulonephritis	2 (10.0)
Polycystic Kidney Disease	4 (20.0)
Other	7 (35.0)
Diabetes N (%)	6 (30.0)
Hypertension N (%)	20 (100)
Cardiovascular Disease N (%)	2 (10.0)
Obstructive Sleep Apnea N (%)	5 (25.0)
eGFR (ml/min/1.73m^2)	75 ± 22
Serum Bicarbonate (mEq/L)	23.4 ± 2.0
Blood Pressure Medication N (%)	
ACEi/ARB	4 (20.0)
Diuretic	1 (5.0)
Calcium Channel Blocker	6 (30.0)

All values are mean ± SD unless otherwise specified. eGFR= estimated glomerular filtration rate.

Table 2: Safety Data with use of Sodium Bicarbonate Therapy in KTRs

Safety Parameter	Placebo	Sodium Bicarbonate	P-value
Systolic Blood Pressure, mmHg			
Baseline	125 ± 10	129 ± 19	
8 weeks	127 ± 16	124 ± 14	
Δ from baseline	2.1 ± 11	−4.4 ± 14	0.17
Diastolic Blood Pressure, mmHg			
Baseline	72 ± 7	75 ± 9	
8 weeks	77 ± 9	73 ± 9	
Δ from baseline	4.6 ± 8	−1.6 ± 9	0.02
Weight, kg			
Baseline	77.7 ± 12.2	78.2 ± 13.0	
8 weeks	77.8 ± 11.6	77.7 ± 11.7	
Δ from baseline	0.1 ± 1.7	-0.6 ± 2.3	0.40
Serum Bicarbonate, mEq/L			
Baseline	23.4 ± 2.1	24.1 ± 1.5	
8 weeks	23.6 ± 1.7	24.54 ± 1.7	
Δ from baseline	0.2 ± 1.7	0.3 ± 1.5	0.93
Serum Potassium, mg/dL			
Baseline	4.0 ± 0.2	4.0 ± 0.3	
8 weeks	3.9 ± 0.2	3.9 ± 0.3	
Δ from baseline	-0.1 ± 0.3	-0.1 ± 0.3	0.95

All values are mean ± SD unless otherwise specified..

- The mean (SD) age, eGFR, and serum bicarbonate of study participants were 52 (17) years, 74.7 (22.4) ml/min/1.73m^2, and 23.4 (2.0) mEq/L respectively (Table 1).
- Serum bicarbonate levels increased by 0.3 mEq/L with sodium bicarbonate therapy (Table 2).
- There is a trend towards improved FMD with sodium bicarbonate therapy when compared to control (Figure 1).
- 24-hour urine NH4 excretion decreased significantly with sodium bicarbonate therapy (mean change -9.1 (11.0) mmol/day, p=0.002).

Conclusions

- Sodium bicarbonate therapy is safe and feasible in KTRs.
- There is a trend towards improvement in FMD with sodium bicarbonate therapy, strengthening the need for larger RCTs to evaluate the effects of sodium bicarbonate therapy in KTRs.

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