




IN CONTEXT

Sodium bicarbonate in kidney transplant recipients: do some apples a day keep the doctor away?

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Metabolic acidosis is a common complication of chronic kidney disease (CKD), and is associated with increased risk for progression to end-stage kidney disease and increased mortality [1]. It is very frequent in kidney transplant recipients (KTRs) (prevalence of 10%–50%) [2] and is more severe in transplanted versus non-transplanted patients of similar kidney function. This could be attributed to several factors, including the pathogenesis of the underlying disease, donor characteristics, immunological features and immunosuppressive agents [2]. Data have underscored the role of calcineurin inhibitors (CNIs) in the process: cyclosporine A induced renal tubular acidosis by blocking the PPIase activity of cyclophylin [3]; tacrolimus affected kidney transport proteins [4]; and CNIs disrupted distal tubular functions [5].

Various studies have evaluated the effects of alkali treatment in CKD patients, most of them demonstrating a benefit in delaying progression of kidney disease [6, 7]. Nevertheless, prospective studies examining the effect of alkali treatment in KTRs have been missing so far. The Preserve-Transplant Study by Mohebbi et al. [8] is a prospective, multicenter, randomized, placebo-controlled, single-blind, phase 3 trial that elegantly presents significant data on the effects of sodium bicarbonate administration in the progression of graft function in KTRs with metabolic acidosis. It included 240 KTRs with an estimated glomerular filtration rate (eGFR) between 15 and 89 mL/min/1.73 m², <15% change in serum creatinine in the last 6 months and serum bicarbonate levels <22 mmol/L. Randomization

assigned 119 and 121 patients to treatment and placebo arms, respectively. One to two capsules containing 500 mg sodium bicarbonate or placebo were given three times daily according to the patient's body weight, and dose was titrated to a maximum of nine capsules a day. The primary outcome was the eGFR slope over the 2-year observation period. Secondary outcomes were the differences in serum bicarbonate, pH, albuminuria and mean blood pressure. CNIs were used in 223 KTRs (93%). At the end of the 2-year period, the eGFR course was not statistically different between the treatment and placebo groups and eGFR slopes were distributed in a similar manner between them in both the intention-to-treat and per-protocol populations. Although sodium bicarbonate corrected acidosis, the mean difference in eGFR between the two groups was only 0.032 mL/min/1.73 m² per year (95% confidence interval –1.644 to 1.707). A subgroup analysis revealed no difference in eGFR slopes and a sensitivity analysis further confirmed results (Fig. 1). Adverse events, including rates of hypertension and volume overload, were also similar.

The failure to demonstrate benefit in the transplantation setting could be partly explained by the mild acidosis and its relatively short duration or by possible different mechanisms of acidosis in the KTRs enrolled. Nevertheless, for the first time, the Preserve-Transplant Study provides compelling evidence that sodium bicarbonate treatment in KTRs with metabolic acidosis does not delay the progression of graft dysfunction over a 2-year period. Although safe, sodium bicarbonate should

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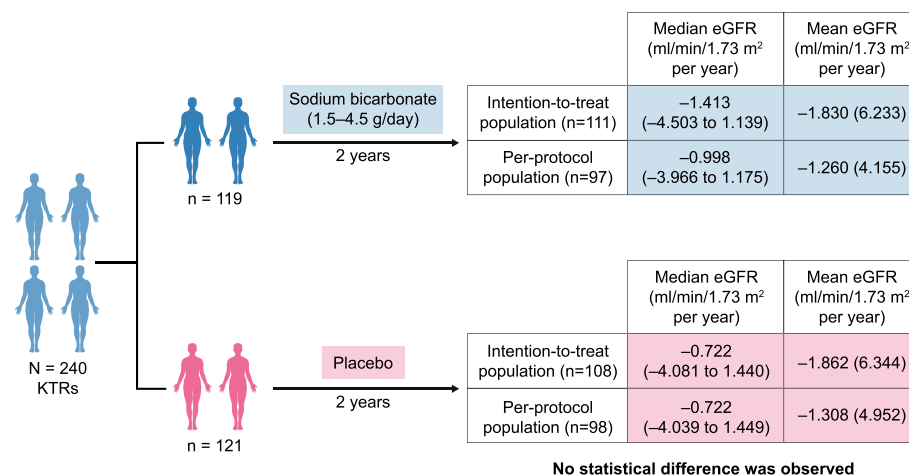


Figure 1: The Preserve-Transplant Study. A total of 240 KTRs were randomly assigned to treatment (sodium bicarbonate) and placebo groups. The calculated yearly eGFR slopes over the 2-year treatment period were a median -0.722 mL/min/1.73 m² per year (IQR -4.081 to 1.440) and mean -1.862 mL/min/1.73 m² (SD 6.344) per year in the placebo group versus median -1.413 mL/min/1.73 m² (IQR -4.503 to 1.139) and mean -1.830 mL/min/1.73 m² (SD 6.233) per year in the sodium bicarbonate group (Wilcoxon rank sum test $P = .51$; Welch t-test $P = .97$). The per-protocol analysis also did not show difference in eGFR slopes in both groups. SD: standard deviation; IQR: interquartile range.

not be recommended to preserve graft function. In this already drug-burdened population, decreasing the daily number of pills is important and should be considered in daily practice. Studies investigating the effects of alkali agents on other manifestations in acidotic KTRs, e.g. musculoskeletal, are needed.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

S.M. and E.F. designed the work. S.M. prepared the first draft which was critically revised by E.F. S.M. and E.F. approved the final version to be submitted.

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