Critical Review Form
Therapy

Management of Hyperkalemia with a Cation-Exchange Resin, *NEJM* 1961; 264:115-119

Objective: **To describe "the use of a sulfonic polystyrene cation-exchange resin in the sodium cycle [Kayexalate] for the control of hyperpotassemia in both acute and chronic renal disease." (p.115)**

Methods: **Thirty-two patients with either acute or chronic renal disease at an unstated hospital (Bellevue?) over an unspecified period of time were observed after the administration of Kayexalate for hyperkalemia. No standard dosing or treatment intervals were used since "dosage varied with the clinical situation and the degree of hyperkalemia." (p. 116) Orally, Kayexalate was given in divided doses totaling 20-60 grams/day dissolved in 100-200 mL of water. Rectally, Kayexalate was administered as 10-40 gram doses suspended in water with repeat doses in 4-12 hours if necessary.**

Potassium intake was limited with a high calorie, low potassium diet. The use of other therapeutic agents (insulin, bicarbonate) depended on the clinical situation. Sodium and potassium levels were assessed using the Baird atomic flame photometer. Carbon dioxide was measured using the Van Slyke Manometer.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No, patients were not randomized. Therefore, there is significant potential for selection bias and unequal prognostic characteristics between groups and other unmeasured confounding variables.
2.	Was randomization concealed (blinded)?	No. Clinicians, patients, families, and outcome assessors were not blinded to the treatment allocation arm.

3.	Were patients analyzed in the groups to which they were randomized?	There was no randomization. Hence, an intention-to-treat analysis is not meaningful.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	The investigators are not attempting to compare two groups in this descriptive observational analysis. None-the-less, in order for clinicians to confidently apply these findings to other patients additional prognostic details are needed. What was the age of patients? Creatinine clearance? Duration of hyperkalemia before Kayexalate was administered?
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes, so bias is possible.
2.	Were clinicians aware of group allocation?	Yes, so bias is possible.
3.	Were outcome assessors aware of group allocation?	Yes, so bias is possible.
4.	Was follow-up complete?	No lost to follow-up was reported.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 22 patients received Kayexalate orally, 8 rectally, and 2 were given Kayexalate by mouth over a period of months. • 23 patients decreased serum K+ by at least 0.4 mEq/L with a mean of 1.0 mEq/L via oral route and 0.8 mEq/L by rectal route. • Kayexalate was ineffective in 2 patients (both post-operative) both of whom also received insulin and bicarbonate.

		• Constipation after oral Kayexalate was occasionally observed (no details provided), but fecal impaction was not noted. • The authors do not report on the effect of Kayexalate upon serum sodium. • Plasma carbon dioxide levels were generally not affected by Kayexalate.
	How precise was the estimate of the treatment effect?	No statistical analyses or confidence intervals are provided.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Uncertain. As noted in Table 1, these were a mix of sepsis-related acute renal failure (N=6), post-operative ARF (N=7), etiology unknown ARF (N=2), diabetic glomerulosclerosis (N=3), and acute/chronic glomerulonephritis (N=8), and chronic pyelonephritis (N=3). Readers are left uncertain about age, co-morbid illness burden, duration of hyperkalemia or creatinine clearance. Extrapolating these results to the general ED population in whom we treat with Kayexalate for hyperkalemia (African-American, dialysis patients with chronic diabetic or hypertensive kidney disease) may lack external validity.
2.	Were all clinically important outcomes considered?	No patient-centric outcomes were presented or hypothesized. Were hyperkalemia-related fatalities avoided? Did patients feel better with a potassium lowered by a mean 1 mEq/L or did they feel worse because of "occasional" constipation?

3.	Are the likely treatment benefits worth the potential harm and costs?	Based upon the limitations highlighted below, one cannot make any confident conclusions based upon this study.

Limitations

1) **No randomization or blinding, hence significant potential for bias secondary to unmeasured confounding variables.**
2) **Little description of the patient population (inclusion/exclusion criteria, duration of hyperkalemia, ECG changes, age, race) so impossible to judge the external validity of these results for ED settings.**
3) **No confidence intervals or tests for statistical significance.**
4) **No *a priori* or *post-hoc* power calculation so potential for Type I or Type II error.**
5) **No report on patient-centric outcomes. How many had constipation? Does a K+ of 6.0 mEq/L matter if the patient does not experience symptoms and no adverse events occur?**

Bottom Line

Non-randomized, poorly described trial that suggests that most patients with acute or chronic kidney disease will reduce their serum potassium levels after oral or rectal Kayexalate alone (mean decrease 1 mEq/L). Potassium levels will continue to decrease or hold stable for 24 hours after Kayexalate is stopped. Some patients will experience constipation. Larger trials that control for etiology, severity, and duration of renal dysfunction in ED-relevant patients with hyperkalemia are needed, but since 50 years have passed since this publication and Kayexalate is considered the standard of care in all leading EM textbooks for the acute management of hyperkalemia, insufficient equipoise may exist for IRB's to approve such an RCT.