UAMS EM Journal Club
July 2020 Summary
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Sodium Zirconium Cyclosilicate or Kayexalate Compared to Placebo in Treatment of Hyperkalemia

Clinical Bottom Line:

Current evidence does not support the use of either kayexalate or sodium zirconium cyclosilicate for the emergent reduction in serum potassium in the patients with acute hyperkalemia, as reductions in serum potassium were not necessarily clinically significant and we are not confident in the safety of these therapies.

PICO Question

In patients with hyperkalemia, are either Kayexalate or Sodium Zirconium Cyclosilicate, compared with placebo, effective in short-term management of hyperkalemia?

Background:

Hyperkalemia is a common electrolyte abnormality that presents to the Emergency Department and requires emergent treatment. Although dialysis is an ideal way to treat hyperkalemia, there are several logistical barriers that prevent patients from receiving this therapy in a timely manner. Potassium binders such as Kayexalate are not an uncommon treatment, however the potential gastrointestinal side effects remain a concern and evidence of efficacy is questionable. Sodium Zirconium Cyclosilicate (SZC) is a new potassium binder that may show more promising outcomes for treatment of hyperkalemia.

Trial 1:

Peacock et al. “Emergency Potassium Normalization Treatment Including Sodium Zirconium Cyclosilicate” *Acad Emerg Med*. 2020; 27(6):475-486

Link:

https://onlinelibrary-wiley-com.libproxy.uams.edu/doi/abs/10.1111/acem.13954

Validity Rating:

Low risk of bias

The Basics:

This study was a multicenter/international, randomized, double-blinded, placebo controlled, parallel group, phase II study of hyperkalemia treatment with SZC in the ED setting. Sodium Zirconium Cyclosilicate (SZC) is a potassium binder that acts throughout the entire GI tract (upper and lower) which is a key difference from Kayexalate, which only works in the colon. SZC increases fecal potassium excretion and has been observed in several clinical trials to rapidly lower K+ within 1 hour. A SZC oral suspension is currently approved in US and Europe for treatment of

hyperkalemia, but not currently approved as an emergency treatment for life threatening hyperkalemia. Due to difficulties in current definitive treatment of hyperkalemia, it is an interesting question, is SZC a useful emergent treatment? Patients were included in the study if they had a serum K >5.8 and were randomized into two groups, SZC group vs. placebo. Each group received weight based insulin + glucose in addition to TX vs. Placebo

Inclusion Criteria:
Patient ages 18 or older and admitted to the ED, had a whole blood potassium equal to or greater than 5.8 mml/L as measured using i-STAT device and confirmation by lab serum potassium assessment.

Exclusion Criteria:
Possible pseudohyperkalemia, life-threatening cardiac arrhythmias, dialysis within 4 hours of randomization, medical conditions other than hyperkalemia that would require immediate treatment in the hospital, hyperkalemia caused by a medical condition that would be best treated with therapy targeting underlying cause, contraindication to treatment with insulin and glucose, contraindication to treatment with rapid-acting insulin, treatment with SZC, SPS, calcium polystyrene sulfonate, or patiromer within previous 24 hours, received more than one course of insulin since arriving at the hospital, pregnancy, breastfeeding, allergy SZC.

Primary Outcome:
To assess the effect of SZC (plus insulin and glucose) vs. placebo (plus insulin and glucose) on decreasing potassium level at 4 hours after the first dosing.

Secondary Outcome:
Effect of SZC vs. placebo on the proportion of patients responding to therapy with endpoints defined as

- Proportion of patients with serum K+ <6 mmol/L between 1 and 4 hours, serum K+ <5.0 at 4 hours, and without additional therapy administered for hyperkalemia from 0 to 4 hours
- Mean change from baseline in serum K+ at 1 and 2 hours after the start of dosing
- Proportion of patients with serum K+ 3.5-5.0 mmol/L (normokalemia), <5.5 mmol/L, or <6.0 mmol/L at 1,2, and 4 hours after start dosing
- Proportion of patients receiving additional potassium-lowering therapy within 4 hours after the start of dosing

Results:

- For the primary outcome, the least square mean serum K+ change from baseline to 4 hours was -0.41 (+/- 0.11) mmol/L and -0.27 (+/- 0.10)

mmol/L with SZC and placebo (difference =-0.13 mmol/L, 95% CI= -0.44 to 0.17).

- There was a greater reduction in mean serum K+ form baseline with SZC compared to placebo at 2 hours: -0.72 (+/- 0.12) vs. -0.36 (+/- 0.11) mmol/L (LSM difference -0.35 mmol/L , 95% CI = -0.68 to -0.02).
- In the SCZ group, a lower proportion of patients received additional potassium-lowering therapy compared to the placebo group at 0 to 4 hours compared to placebo (15.6% vs. 30.6%, odds ration= 0.40, 95% CI =0.09 to 1.77).
- Proportion of patients experiencing adverse events was similar between SZC and placebo group.

Limitations/Bias:

1. Sample size was too small (only 70 patients)
2. There were no clear guidelines for dosing additional “rescue” therapy and thus this was up to the discretion of the clinician
3. There was a lot of missing data (iSTAT labs and lab values)
4. High withdrawal rate
5. The reduction in serum K is not necessarily clinically significant.

Trial 2:

Batterink, J., Lin, J., Au-Yeung, S. H., & Cessford, T. (2015). Effectiveness of Sodium Polystyrene Sulfonate for Short-Term Treatment of Hyperkalemia. The Canadian Journal of Hospital Pharmacy, 68(4). doi:10.4212/cjhp.v68i4.1469

Link:

https://pubmed.ncbi.nlm.nih.gov/26327703/

Validity Rating:

Low risk of bias

The Basics:

This single center retrospective observational study was preformed in an attempt to evaluate the efficacy of sodium polystrene sulfonate (SPS), also known as kayexalate. Given the potential life threatening side effect and lack of evidence showing efficacy of SPS in the management of hyperkalemia its use has come into question. This group enrolled patients admitted to an internal medicine service of a tertiary care center with asymptomatic hyperkalemia and attempted to observe the effects of SPS on potassium levels in 4-24 hours.

Inclusion Criteria:

Patients aged 19 years or older with serum potassium levels of 5.0-5.9 mmol/L admitted to medicine service between January 2011 and May 2012.

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Exclusion Criteria:
Hyperkalemia at the time of admission (unless greater than 48 hours since admission with interval normalization of potassium level)
Lack of followup serum potassium measurement within 24 h after the index measurement
Acute or chronic renal failure
Medication history with missing or unclear information
Medication administration with missing or unclear information about SPS treatment
Potassium-altering dietary or medication change during the index hyperkalemia episode

Primary Outcome:
Mean change in serum potassium levels in 6-24 hours when compared to no intervention.

Secondary Outcome:
Identify any potential relationship between dose and of SPS and magnitude of serum potassium reduction. Additionally, the occurrence of adverse events associated with SPS therapy.

Results:
- For the primary outcome, the mean change on serum potassium was 0.14 mmol/L (-0.44 +/- 0.29 mmol/L versus -0.58 +/- 0.39 mmol/L; p=0.026)
- There was no significant change in the serum potassium level between the groups that received 15g or 30g SPS (-0.51 versus -.066 mmol/L)
- Only one patient was found to have a documented adverse event that was later found to be unrelated to SPS administration

Limitations/Bias:
- Due to the study design, retrospective, a risk for both bias and confounding is present
- Follow up potassium levels for control and intervention group were not evenly distributed between 6-24 hours with the control group having a greater percentage draw at 24 hours leaving a potential for SPS being masked.
- Due to study design, dictation of SPS dose was impossible leading to potential of missing a dose correlated difference in effect
- Given relatively small study size and rate of adverse events a correlation could have been missed.