Critical Review Form
Meta-analysis

Emergency interventions for hyperkalaemia, *Cochrane Database Systematic Rev*. 2005; Issue 2. Art. No.: CD003235. DOI: 10.1002/14651858. CD003235. Pub2

Objective: **"To summarize RCTs and quasi-RTCs of acute interventions (calcium, beta-2 agonists, bicarbonate, ion-exchange resins, and dialysis) in the treatment of patients with hyperkalaemia, with respect to the outcomes: serum potassium ECG changes, arrhythmia, adverse effects of therapy and death." (p. 2).**

Methods: **Two reviewers conducted a database search of MEDLINE (1966-2003), EMBASE (1980-2003), Cochrane Library, Cochrane renal group's specialized register of trials, and Sci Search. Titles and abstracts were reviewed independently and full text articles were obtained when potentially relevant. Final decisions for inclusion were made independently by the two reviewers based upon the full text. Article inclusion criteria were adults > 1 month old enrolled into an RCT, quasi-RCT (allocation by alternating date of birth or other predictable method), and randomized crossover studies. At least one intervention had to be given to 5 subjects. Artificially induced hyperkalaemia was excluded. Outcome measures included plasma or serum potassium, arrhythmia, ECG changes, adverse effects of interventions, and death.**

For the planned meta-analyses, a random-effects model was to be used combining serum potassium at 30^{-} and 60^{-} minutes into one group. Heterogeneity was assessed with the Cochrane's chi-square and I^2. If duplicate data appeared in multiple publications, only data from the most recent publication was used.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes – what is the effectiveness for emergency interventions to treat hyperkalaemia?
2.	Was the search for relevant studies details and exhaustive?	Yes – multiple electronic data search engines as well as scientific abstracts, multiple prominent textbooks, and ACP JC and Evidence Based Medicine.
3.	Were the primary studies of high methodological quality?	No. Focusing only on the single Kayexalate study, it is a randomized cross-over trial of just six patients none of whom had extremely high hyperkalaemia or hemodynamic instability. (p. 23).
4.	Were the assessments of the included studies reproducible?	Yes, two authors assessed trials for allocation concealment, blinding of participants, intention-to-treat analysis and completeness of follow-up.
II.	***What are the results?***	
1.	What are the overall results of the study?	Again, focusing on the single Kayexalate trial: "No differences in serum potassium were observed at four hours when resin was compared with placebo." (p. 10). **Comparison 5. Sodium polystyrene sulphonate versus placebo** **Outcome or subgroup title** / **No. of studies** / **No. of participants** / **Statistical method** / **Effect size** 1 Serum potassium — 1 — Mean Difference (IV, Random, 95% CI) — Totals not selected 1.1 0 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.11 [-0.95, 0.73] 1.2 240 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.18 [-1.15, 0.79] 1.3 480 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.28 [-1.15, 0.59] 1.4 720 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.42 [-1.29, 0.45] **Comparison 6. Phenolphthalein-docusate versus placebo** **Outcome or subgroup title** / **No. of studies** / **No. of participants** / **Statistical method** / **Effect size** 1 Serum potassium — 1 — Mean Difference (IV, Random, 95% CI) — Totals not selected 1.1 0 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.08 [-1.07, 0.91] 1.2 240 minutes — 1 — Mean Difference (IV, Random, 95% CI) — 0.16 [-1.18, 1.50] 1.3 480 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.07 [-1.07, 0.93] 1.4 720 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.09 [-1.28, 1.10]

		Comparison 7. Phenolphthalein-docusate plus sodium polystyrene sulphonate versus placebo **Outcome or subgroup title** / **No. of studies** / **No. of participants** / **Statistical method** / **Effect size** 1 Serum potassium — 1 — Mean Difference (IV, Random, 95% CI) — Totals not selected 1.1 0 minutes — 1 — Mean Difference (IV, Random, 95% CI) — 0.03 [-0.80, 0.86] 1.2 240 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.02 [-1.18, 1.14] 1.3 480 minutes — 1 — Mean Difference (IV, Random, 95% CI) — Not estimable 1.4 720 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.06 [-1.13, 1.01] **Comparison 8. Sorbitol plus sodium polystyrene sulphonate versus placebo** **Outcome or subgroup title** / **No. of studies** / **No. of participants** / **Statistical method** / **Effect size** 1 Serum potassium — 1 — Mean Difference (IV, Random, 95% CI) — Totals not selected 1.1 0 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.05 [-1.04, 0.94] 1.2 240 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.13 [-1.34, 1.08] 1.3 480 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.27 [-1.33, 0.79] 1.4 720 minutes — 1 — Mean Difference (IV, Random, 95% CI) — -0.43 [-1.52, 0.66]
2.	How precise are the results?	All 95% CI for the mean change in the potassium concentration crossed zero (see above)
3.	Were the results similar from study to study?	There was only one study of Kayexalate
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	"Though resins are widely used clinically, there was no randomized evidence for their efficacy in an emergency setting, and one study showed no benefits." (p. 16) "A RCT of sodium polystyrene sulfonate (Kayexalate) and of calcium resonium, examining the time course of action of those agents would be of value." (p. 18)
2.	Were all patient important outcomes considered?	No. "All the studies reported surrogate outcome for efficacy, and not all commented on clinically-important adverse events." (p. 17) Clinically important outcomes would include ECG changes, dysrhythmia, arrest and mortality.
3.	Are the benefits worth the costs and potential risks?	No. "There is no randomized evidence that potassium-exchange resins are effective. In the absence of gastrointestinal pathology, these agents are safe, and may be instituted for their possible effects at 24 hours, but should not be relied upon for their rapid effects." (p. 18) However, as noted by the SR authors none of the trials assessed harm as an outcome and for Kayexalate the SR authors neglect to mention the associated risk of colonic necrosis and perforation (Gerstman 1992, Rashid 1997, Roy-Chaudhury 1997).

Limitations

1) **Single non-blinded study of non-emergent (potassium less than 6 mEq/L, no noted ECG changes) ESRD patients limits external validity for the hyperkalemic patients usually treated in the ED.**
2) **Potential publication bias.**
3) **No discussion of potential harms of Kayexalate.**
4) **Incomplete assessment of the single Kayexalate study beyond four hours. Although subjects were given potassium in a meal, it was a standard dose of potassium without any other food or medications permitted. Kayexalate probably affects serum potassium levels beyond 4 hours.**

Bottom Line

No randomized evidence that potassium-exchange resins (Kayexalate) are effective exists. In the absence of an ileus or obstruction, these agents may be safe but should not be relied upon for rapid reductions in potassium. "A RCT of sodium polystyrene sulfonate (Kayexalate) and of calcium resonium, examining the time course of action of these agents would be of value." (p. 18)