UAMS EM Journal Club
February 2022 Summary
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Evaluating the rate of adverse effects of alternative low dose insulin in the treatment of hyperkalemia when compared to traditional dosing

Clinical Bottom Line:
Low dose (less than 10 units) insulin consistently shows a lower adverse effect rate when used to treat hyperkalemia, specifically lower rates of hypoglycemia or severe hypoglycemia. Improved outcomes are seen particularly in patients with end-stage renal disease. There is limited, if any, difference in potassium lowering effects when using a lower dose.

PICO Question:
In emergency department patients with hyperkalemia, does the use of low dose insulin (less than 10 units) compared with traditional dosing (10 units) cause fewer adverse events, such as hypoglycemia?

Background:
Hyperkalemia is a relatively common laboratory abnormality encountered in the emergency department. It is typically related to renal dysfunction, however there are other etiologies such as medication side effects, adrenal insufficiency, and rhabdomyolysis. The most feared complication of hyperkalemia is cardiac arrhythmias, which can be fatal if untreated. The treatment of hyperkalemia is multifaceted. Treatment involves first stabilizing the cardiac membranes with IV calcium if EKG changes are present. Subsequently, treatments focus on either reducing potassium from the body or reducing available circulating extracellular potassium. The most practical methods in the ED utilize the later treatment strategy using insulin, albuterol, and sodium bicarbonate. Traditionally, 10 units has been used for rapid reduction of serum potassium. However, can lead to hypoglycemia, especially in those with CKD. Optimal insulin dosing is unclear.

Trial 1:
Moussavi et. al. "Comparison of IV Insulin Dosing Strategies for Hyperkalemia in the Emergency Department" *Critical Care Explorations*. 2020 April; 2(4): e0092

Pubmed link:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7188424/

Risk of Bias: Moderate risk of bias due to retrospective nature and limited details of chart review

The Basics:

This was a retrospective chart review of a single academic emergency department evaluating the outcomes after 10 units vs less than 10 units were given in hyperkalemia patients. The primary endpoint was hypoglycemia within 12 hours.

Methods:
This study included 700 adult patients that were treated for hyperkalemia over roughly a 5-year period. It is not clear who performed the chart review based on the publication or what training they received. Patients were excluded that did not have a baseline potassium level, were not hyperkalemic >5mMol/L, had no post treatment potassium level, had no blood glucose level after treatment, or received greater than 10 units of insulin. Those that received 10 units were compared with those that received less than 10 units of insulin. The primary outcome of hypoglycemia was measured over a 12 hour period. Secondary outcomes included time to hypoglycemia, nadir serum glucose, frequency of severe hypoglycemia, change in serum potassium, IV dextrose requirements, use of other agents, length of ICU stay, length if hospital stay, and in-hospital mortality. Univariate and subsequent multivariate analysis were used to evaluate predictors of hypoglycemia.

Results:
Patients that were treated with less than 10 units of insulin for hyperkalemia had a significantly lower risk of hypoglycemia (11.2% vs 17.6% p=0.008) with a NNT of 15.6. Insulin dose, age, dialysis dependence, history of DM and initial serum glucose were more strongly associated with hypoglycemia based on univariate analysis. Multivariate analysis found that only insulin dose, dialysis dependency, and initial serum glucose were associated with hypoglycemia.

Limitations/Bias:
This paper is inherently limited by the fact that it is retrospective and only included adult patients. Additionally, the specifics of the actual chart review were not discussed in depth, such as who performed the review and what methods they specifically used. Also, the dose less than 10 was not stratified therefore it is not clear what specific dose is safest in these patients.

Trial 2:
Moussavi K, Garcia J, Tellez-Corrales E, Fitter S. Reduced alternative insulin dosing in hyperkalemia: A meta-analysis of effects on hypoglycemia and potassium reduction. *Pharmacotherapy*. 2021;41: 598–607.

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/33993515/

The Basics:
This was a metaanalysis of retrospective cohort studies that compared 10 units vs an alternative dosing regimen including 5 units, 0.1 units/kg, and <10 units. This trial looked at serum potassium reduction as well as incidents of hypoglycemia.

Methods:
Ten retrospective cohort studies were included with low to moderate risk of bias based on Cochrane Risk of Bias Assessment Tool and Newcastle-Ottawa scales. The studies compared

10 units of insulin versus alternate dosing strategy including 5 units, 0.1 units/kg, and <10 units of insulin. Studies were identified through database search through pubmed, OVID, CENTRAL, and clinicaltrials.gov with 139 studies identified. 125 studies were excluded if they were not in English, had no dose for comparison, were not a cohort or RCT, in an animal model, or in an OR setting. Analyses included pooled odds ratios and outcomes were plotted on forrest plots. Heterogeneity was assessed by calculating the Z score as well as evaluation with leave-one-out analysis.

Results:
Lower dosing strategies (< 10 units of insulin) demonstrated lower pooled odds of hypoglycemia (OR 0.55, 95% CI 0.43-0.69, I^2=8%), resulting in a NNT of 13. Similarly, there was a lower risk of severe hypoglycemia (OR 0.41, 95% CI 0.27-0.64, I^2=0%) with a NNT of 31 to prevent one episode of severe hypoglycemia. There was no significant difference in potassium reduction (mean difference -0.02 mmol/L, 95% CI -0.11 – 0.07). There were no differences in hospital mortality, ICU length of stay, or hospital length of stay.

Limitations/Bias:
Inherit limitations of meta-analysis of retrospective cohort studies. Variety between studies of alternate dosing regimen, definition of hypoglycemia and severe hypoglycemia, and time point of glucose measurements.