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SHORT REPORT

A Retrospective Study of Patiromer as Adjunct to Insulin Therapy for Acute Hyperkalemia in the Emergency Department

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Objective: To investigate the clinical utility of administering patiromer as an adjunct to insulin for potassium reduction in patients presenting to the emergency department (ED) with hyperkalemia.

Methods: This retrospective cohort study used electronic health record data to identify adults treated with at least one intravenous dose of regular insulin for hyperkalemia within the ED. Patients who were administered patiromer within one hour before or after their insulin dose were categorized as the intervention group. Matching was performed at a 1:1 ratio. The primary outcome, mean change in potassium from baseline to the latest value within the 4–12 hour interval, was compared. Secondary outcomes included net clinical benefit, defined as the mean difference in the number of potassium-lowering interventions minus the change in potassium.

Results: The final analysis included 133 patients treated with patiromer plus insulin and 133 patients treated with insulin alone. Participants had a mean age of 71 years; 43% were female, 31% self-identified as Black, and 38% self-identified as Latinx. No significant changes were observed in potassium from baseline (mean levels 6.2 mEq/L in each group) to the 4–12 hour time frame (patiromer: −0.90 mEq/L, n=78 vs insulin-only: −0.98 mEq/L, n=81; p = 0.51). The calculated net clinical benefit of potassium reduction was −0.25 in favor of the patiromer plus insulin group; however, this difference did not reach statistical significance. In the subgroup of eGFR >30 mL/min, patiromer group received numerically less potassium-lowering interventions (0.63 vs 1.12, p = 0.057).

Conclusion: In this study of patients with acute hyperkalemia in the ED setting, concurrent administration of patiromer did not result in more sustained potassium reduction compared to insulin alone in the overall cohort. The trend in favor of adjunct patiromer in the subgroup with adequate renal function warrants further investigation.

Keywords: patiromer, hyperkalemia, emergency department, insulin, renal impairment

Introduction

Hyperkalemia is a prevalent and potentially life-threatening electrolyte imbalance. In the United States, the estimated prevalence of hyperkalemia, defined as a serum potassium concentration exceeding 5.5 mmol/L, is approximately 3.6% within the emergency department (ED).[1] Notably, a higher prevalence is reported among patients with conditions such as heart failure, those recently initiated on renin-angiotensin system inhibitors and aldosterone antagonists, and individuals with chronic kidney disease or acute kidney injury.[2,3]

Prior studies have demonstrated that the administration of patiromer monotherapy leads to rapid reduction of serum potassium levels in patients not receiving concomitant insulin.[4–6] This effect initiates within the initial 0–6 hours (mean draw time of 2.9 hours) and endures for at least 24 hours.[7] This observed reduction in potassium levels is of particular interest in the context of the ED where patients frequently present with acute episodic hyperkalemia.[3] Among the available treatment options, injectable insulin stands out as a commonly employed approach due to its ability to rapidly induce intracellular potassium shifts. However, a limitation of this method is the diminishing effect observed after

Received: 18 July 2024
Accepted: 20 November 2024
Published: 5 December 2024

approximately 4–6 hours.[8] Consequently, healthcare practitioners often find it necessary to administer supplementary doses of potassium-lowering agents.

Given the pharmacokinetics of patiromer, it presents itself as a promising candidate for co-administration with insulin. This combined approach holds the potential to sustain the trajectory of potassium reduction beyond the initial 4-hour window typically achieved with insulin alone. The potential advantage of this combined strategy is maintaining a more prolonged reduction in potassium levels and reducing the reliance on frequent re-dosing of insulin, which has been associated with higher risk of hypoglycemia and death.[9] Such benefits hold particular significance within the resource-constrained environment of the ED.

An open-label, randomized pilot study (REDUCE), showed that patiromer plus standard of care (insulin and albuterol) significantly reduced serum potassium levels to a greater extent than standard of care alone at 2 hours, however there were no significant differences at 4 or 6 hours.[10] A larger, double-blind, randomized controlled trial, Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalemia Management (PLATINUM), is currently underway to further investigate the advantages of this combined approach in the ED setting.[11] In the interim, there remains a gap in evidence on the effectiveness of co-administering patiromer with insulin in an acute care setting that this observational study aims to address. Additionally, this study provides a unique opportunity to derive valuable insights from well-designed investigations rooted in local, real-world evidence within a single health system and benchmark these findings against the clinical trial results.

The objective of our study is to assess whether co-administering patiromer with insulin for the management of episodic hyperkalemia in the ED enhances potassium reduction during the 4–12 hours following administration. Furthermore, we aim to determine whether this combined approach reduces the need for adjunct interventions (such as insulin, dialysis, potassium binders, and albuterol) following the initial treatment, in comparison to using insulin alone as the primary treatment strategy.

Methods

Study Design

This retrospective, observational cohort study was conducted utilizing electronic health record (EHR) data and the target trial emulation framework.[12] The study followed the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) reporting guideline, an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[13]

Study Population

The study included patients that presented to the ED for any reason between July 2018 and July 2023, were found to have hyperkalemia, defined as a serum potassium level exceeding 5.0 mEq/L, and treated with at least one intravenous dose of regular insulin (5–12 units) for hyperkalemia. Individuals with missing baseline data, chronic use of potassium binders (defined as an outpatient prescription in the preceding 6 months), other forms of insulin therapy (eg, long acting or infusion) administered in the ED, or co-administration of potassium binders other than patiromer were excluded.

Intervention and Control Groups

Patients who were administered patiromer within one hour before or after their insulin dose were categorized as the intervention group. Patients without an order for patiromer within the EHR were allocated to the control group. Matching was performed at a 1:1 ratio within each group, employing coarsened exact matching based on baseline serum potassium elevation, insulin dose, dialysis status, age, estimated glomerular filtration rate (eGFR), and prior exposure to renin-angiotensin-aldosterone system inhibitors (RAASi).

Data Collection and Primary Outcome

Potassium levels were collected from time zero (one hour after insulin administration) and up to 24 hours later. The primary outcome, mean change in potassium levels from baseline to the latest value within the 4–12 hour interval, was compared between the intervention and control groups.

Secondary Outcomes

Multiple secondary outcomes were evaluated. Adjunct interventions for potassium lowering within the 12 hours following insulin administration were compared between groups, which included supplementary intravenous insulin doses, nebulized albuterol, subsequent administrations of potassium binders, and hemodialysis sessions. To align our findings with the primary endpoint of the PLATINUM trial, we calculated a group-level net clinical benefit marker, defined as the mean difference in the number of interventions minus the change in serum potassium. We also assessed the incidence of hypokalemia (defined as potassium levels <3.5 mEq/L) as our safety endpoint. Two pre-specificized subgroup analyses were conducted—one restricted to patients with baseline potassium levels >5.8 mEq/L (consistent with the inclusion criteria of the PLATINUM trial), and another restricted to patients with an eGFR >30 mL/min.

Statistical Analysis

Continuous measures, such as potassium reduction and the total count of additional interventions, were assessed using *t*-tests. Categorical variables were analyzed using the Chi-squared test. Analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

In accordance with the principles of the Declaration of Helsinki, this study was approved by the Albert Einstein College of Medicine Institutional Review Board, with a waiver of informed consent due to retrospective nature of the chart review. All data were stored and analyzed on an encrypted platform to maintain security and patient confidentiality.

Results

Of the 2689 eligible patients treated with insulin for hyperkalemia during the study period, the final analysis included 133 patients treated with patiromer plus insulin matched with 133 patients treated with insulin alone. Pre-specified baseline variables were similar between the two groups (see Table 1). Participants had a mean age of 71 years (SD 14 years); 43%

Table 1 Baseline Demographics

	Overall	Insulin	Insulin and Patiromer	p-value
	266	133	133	
Age, years, mean (SD)	70.89 (13.95)	70.98 (13.66)	70.81 (14.28)	0.921
Ethnicity, n (%)				0.889
Spanish/Hispanic/Latino	101 (38.0)	50 (37.6)	51 (38.3)	
Not Spanish/Hispanic/Latino	160 (60.2)	81 (60.9)	79 (59.4)	
Other	5 (1.9)	2 (1.5)	3 (2.3)	
Asian	10 (3.8)	5 (3.8)	5 (3.8)	
Race, n (%)				0.789
Black or African-American	83 (31.2)	39 (29.3)	44 (33.1)	
White	69 (25.9)	38 (28.6)	31 (23.3)	
Other	104 (39.1)	51 (38.3)	53 (39.8)	
Sex, n (%)				1
Male	151 (56.8)	76 (57.1)	75 (56.4)	

(*Continued*)

Table 1 (Continued).

	Overall	Insulin	Insulin and Patiromer	p-value
EGFR, mean (SD)	34.04 (28.48)	34.20 (28.47)	33.87 (28.59)	0.925
EGFR category, n (%)				0.895
<15 mL/min	89 (33.5)	45 (33.8)	44 (33.1)	
15 to 29 mL/min	49 (18.4)	24 (18.0)	25 (18.8)	
30 to 45 mL/min	64 (24.1)	32 (24.1)	32 (24.1)	
45 to 60 mL/min	24 (9.0)	10 (7.5)	14 (10.5)	
>60 mL/min	40 (15.0)	22 (16.5)	18 (13.5)	
Diabetes mellitus, n (%)	119 (44.7)	56 (42.1)	63 (47.4)	0.459
Heart failure, n (%)	78 (29.3)	37 (27.8)	41 (30.8)	0.686
Dialysis-dependent ESKD, n (%)	36 (13.5)	18 (13.5)	18 (13.5)	1
Hemodialysis order at baseline, n (%)	20 (7.5)	10 (7.5)	10 (7.5)	1
Previous RAASi therapy, n (%)	38 (14.3)	19 (14.3)	19 (14.3)	1
Baseline potassium, mEq/L, mean (SD)	6.20 (0.52)	6.19 (0.52)	6.20 (0.53)	0.798
Initial insulin dose of 5 units, n (%)	128 (48.1)	64 (48.1)	64 (48.1)	1
Initial insulin dose of 8–12 units, n (%)	138 (51.9)	69 (51.9)	69 (51.9)	1
Coadministration of albuterol, n (%)	102 (38.3)	49 (36.8)	53 (39.8)	0.705
Coadministration of calcium, n (%)	145 (54.5)	74 (55.6)	71 (53.4)	0.805
Patiromer dose, n (%)				
8.4g	88 (66.2)		88 (66.2)	
16.8g	37 (27.8)		37 (27.8)	
25.2g	8 (6.0)		8 (6.0)	
Patiromer administration route, n (%)				
Gastrostomy tube	4 (3.0)		4 (3.0)	
Oral	127 (95.5)		127 (95.5)	
Oral gastric tube	2 (1.5)		2 (1.5)	

Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation.

were female, 31% self-identified as "Black or African-American", and 38% self-identified as "Spanish/Hispanic/Latino". Approximately 34% of patients exhibited an eGFR of <15 mL/min, and 14% were diagnosed with dialysis- dependent end-stage kidney disease (ESKD). The majority (55%) of patients concurrently received intravenous calcium with their insulin treatment, while 38% were co-administered albuterol at baseline.

No significant changes were observed in potassium levels from baseline (mean levels 6.2 mEq/L in each group) to the 4–12 hour time frame in the overall cohort (patiromer group: −0.90 mEq/L vs insulin-only group: −0.98 mEq/L, p = 0.51, Figure 1). Notably, 40% of patients did not undergo follow-up potassium testing during this interval. The number of additional potassium-lowering interventions did not exhibit significant differences between the groups (1.08 vs 0.80 per

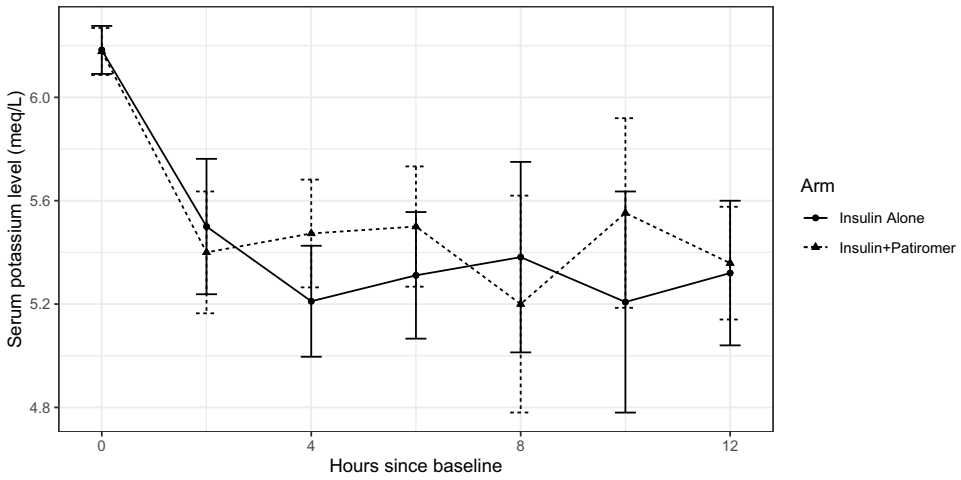

Figure 1 Potassium Trends Over 12 hours Post-Treatment.

person, p = 0.09). The calculated net clinical benefit of potassium reduction was −0.25 in favor of the patiromer plus insulin arm; however, this difference did not reach statistical significance. Furthermore, no significant changes were noted in secondary and safety outcomes (Table 2).

Subgroup analyses (Table 3 and Table 4) were similar to those of primary endpoints. Effects were more pronounced within the subgroup of patients with an eGFR > 30 mL/min. In this subgroup, patients receiving insulin plus patiromer showed a numerical decrease in potassium-lowering interventions (0.63 vs 1.12, p = 0.057) and a statistically significant

Table 2 Treatment Outcomes

	Insulin	Insulin and Patiromer	p-value
	133	133	
Latest potassium reading, 4–12 hours, mEq/L, mean (SD)*	5.23 (0.70)	5.36 (0.73)	0.27
Time to potassium draw, hours, mean (SD)	8.56 (2.36)	8.44 (2.38)	0.731
Latest potassium reading, 4–24 hours, mEq/L, mean (SD)**	5.10 (0.71)	5.19 (0.64)	0.317
Change in potassium at 12 hours, mEq/L, mean (SD)	−0.98 (0.75)	−0.90 (0.85)	0.508
Additional insulin doses administered, mean (SD)	0.53 (0.91)	0.35 (0.58)	0.066
Additional albuterol doses administered, mean (SD)	0.27 (0.66)	0.20 (0.52)	0.355
Additional hemodialysis orders placed, n (%)	11 (8.3)	13 (9.8)	0.831
Total additional interventions, mean (SD)	1.08 (1.53)	0.80 (1.05)	0.094
Additional potassium binder doses administered, mean (SD)	0.20 (0.48)	0.15 (0.36)	0.389
Net clinical benefit, mean (SD)	0.30 (1.84)	0.05 (1.47)	0.344
Hypokalemia incidence at 12 hours, n (%)	0 (0.0)	1 (1.3)	0.985
Hypokalemia incidence at 24 hours, n (%)	1 (1.0)	1 (0.9)	1
No additional interventions, n (%)	68 (51.1)	70 (52.6)	0.902

Notes: Net Clinical Benefit was calculated as the mean difference in the number of interventions minus the change in serum potassium. Total additional interventions includes insulin, albuterol, and potassium binder doses. *40% of patients did not have this reading. **22% of patients did not have this reading.
Abbreviation: SD, standard deviation.

Table 3 Subgroup Analysis of Patients with Baseline Potassium > 5.8 mEq/L

	Insulin	Insulin and Patiromer	p-value
	107	109	
Latest potassium reading, 4–12 hours, mEq/L, mean (SD)*	5.34 (0.69)	5.43 (0.76)	0.453
Time to potassium draw, hours, mean (SD)	8.70 (2.31)	8.71 (2.29)	0.98
Latest potassium reading, 4–24 hours, mEq/L, mean (SD)**	5.17 (0.72)	5.26 (0.61)	0.39
Change in potassium at 12 hours, mEq/L, mean (SD)	−1.02 (0.79)	−1.00 (0.89)	0.894
Additional insulin doses administered, mean (SD)	0.50 (0.92)	0.34 (0.58)	0.136
Additional albuterol doses administered, mean (SD)	0.30 (0.70)	0.23 (0.55)	0.419
Additional hemodialysis orders, n (%)	8 (7.5)	12 (11.0)	0.509
Total additional interventions, mean (SD)	1.09 (1.59)	0.85 (1.10)	0.197
Additional potassium binder doses administered, mean (SD)	0.22 (0.52)	0.17 (0.38)	0.42
Net clinical benefit, mean (SD)	0.38 (1.92)	0.00 (1.54)	0.23
Hypokalemia incidence at 12 hours, n (%)	0 (0.0)	1 (1.6)	0.968
Hypokalemia incidence at 24 hours, n (%)	0 (0.0)	1 (1.1)	1
No additional interventions, n (%)	55 (51.4)	56 (51.4)	1

Notes: Net Clinical Benefit was calculated as the mean difference in the number of interventions minus the change in serum potassium. Total additional interventions include insulin, albuterol, and potassium binder doses. *41% of patients did not have this reading. **22% of patients did not have this reading.
Abbreviation: SD, standard deviation.

reduction in additional potassium binder doses (0.02 vs 0.18 doses per patient, p = 0.009) compared to those receiving insulin alone. The net clinical benefit calculation was even more pronounced in both subgroups (−0.31 in eGFR > 30 and −0.38 in potassium > 5.8 mEq/L), favoring patiromer; however, statistical significance was not achieved in either subgroup.

Table 4 Subgroup Analysis of Patients with Baseline eGFR > 30 mL/min

	Insulin	Insulin and Patiromer	p-value
	60	60	
Latest potassium reading, 4–12 hours, mEq/L, mean (SD)*	5.10 (0.67)	5.19 (0.69)	0.579
Time to potassium draw, hours, mean (SD)	8.10 (2.41)	8.37 (2.49)	0.654
Latest potassium reading, 4–24 hours, mEq/L, mean (SD)**	4.97 (0.57)	5.16 (0.70)	0.171
Change in potassium at 12 hours, mEq/L, mean (SD)	−0.92 (0.66)	−0.81 (0.80)	0.542
Additional insulin doses administered, mean (SD)	0.63 (1.09)	0.38 (0.58)	0.12
Additional albuterol doses administered, mean (SD)	0.30 (0.70)	0.23 (0.53)	0.557
Additional hemodialysis orders, n (%)	0 (0)	0 (0)	NA

(*Continued*)

Table 4 (Continued).

	Insulin	Insulin and Patiromer	p-value
Total additional interventions, mean (SD)	1.12 (1.68)	0.63 (0.99)	0.057
Additional potassium binder doses administered, mean (SD)	0.18 (0.47)	0.02 (0.13)	0.009
Net clinical benefit, mean (SD)	0.19 (1.85)	−0.12 (1.40)	0.443
Hypokalemia incidence at 12 hours, n (%)	0 (0.0)	1 (3.0)	0.965
Hypokalemia incidence at 24 hours, n (%)	0 (0.0)	1 (2.3)	0.973
No additional interventions, n (%)	30 (50.0)	38 (63.3)	0.197

Notes: Net Clinical Benefit was calculated as the mean difference in the number of interventions minus the change in serum potassium. Total additional interventions include insulin, albuterol, and potassium binder doses. *43% of patients did not have this reading. **26% of patients did not have this reading.
Abbreviation: SD, standard deviation.

Discussion

Patiromer is an orally administered ion-exchange resin that binds excess potassium predominantly in the colon where potassium concentration is the highest. Initially studied to manage chronic hyperkalemia,[14] it has recently garnered attention as a potential tool for addressing acute potassium elevations, especially in ED or hospital settings. Although the underlying causes of acute hyperkalemia in acute settings may vary due to clinical etiology and comorbidity, patiromer offers a promising means of sustainably and reliably lowering serum potassium levels, affording clinicians the time and opportunity to address the root causes of hyperkalemia.

In this study, we found that concurrent administration of patiromer did not significantly sustain the reduction of serum potassium levels nor reduced the need for additional interventions in a cohort of ED patients with hyperkalemia when compared to insulin administration alone. In the subgroup of patients with eGFR >30 mL/min, those in the patiromer group required fewer additional potassium-lowering interventions. While this finding did not reach statistical significance, likely due to limited power in the subgroup analysis, it suggests a trend worth noting. This may be because patients with lower renal function were more likely to undergo dialysis, reducing potassium levels independently of pharmacological treatments. Future research should focus on patients who are unlikely to require hemodialysis, as patiromer appears to be most effective for episodic hyperkalemia in this population. In resource-constrained healthcare systems, the burden of additional testing and therapies for acute hyperkalemia can strain already busy ED clinical care. Treating hyperkalemia with insulin is challenging due to the potential for patient harm from misadministration, dosing errors, and treatment-induced hypoglycemia. Therefore, there is a need to find opportunities for improving treatment safety and mitigating the need for additional testing in the management of hyperkalemia.

This study has noteworthy limitations due to the challenges of assessing the comparative effectiveness of potassium lowering in observational study designs. We expected to observe a difference in potassium reduction in the 4–12 hour period, which did not account for additional potassium-lowering interventions if the initial reduction was deemed insufficient. This underscores the importance of testing alternative effectiveness measures, such as the net clinical benefit employed in the PLATINUM trial. Additionally, our study was unable to differentiate ESKD from acute kidney injury based on eGFR data alone. While we used diagnoses to identify patients with ESKD, the discrepancy between eGFR and diagnosis-based estimates suggests some measurement error. We also did not include hypoglycemia as a potential adverse event since it would necessitate building a separate confounding model and matching process apart from the primary endpoint.

In summary, this observational study suggests that the addition of patiromer to insulin does not significantly improve potassium reduction in the overall cohort of patients in the ED with episodic hyperkalemia. However, the observed trend of reduced need for additional potassium-lowering interventions in patients with adequate renal function warrants further investigation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by a research grant from CSL Vifor, Inc as an investigator-initiated study. The views expressed in the submitted article are of the authors and not an official position of the institution or funder.

Disclosures

PG and KD previously served as consultants for CSL Vifor, Inc. LG reports personal fees from Amgen rare disease, outside the submitted work. The authors report no other conflicts of interest to disclose.

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