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A comparison of insulin doses for the treatment of hyperkalemia in patients with renal insufficiency

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Key words: hyperkalemia, insulin, hypoglycemia, renal insufficiency

Running title: Comparison of insulin doses for hyperkalemia

Abstract

Study objective: To compare the safety and efficacy of 5 units versus 10 units of insulin for the treatment of hyperkalemia in patients with renal insufficiency.

Design: Retrospective cohort study.

Setting: Large academic medical center emergency department.

Patients: Between March 1, 2008 and February 29, 2016, 675 patients met the inclusion criteria of age 18 years and older, serum potassium greater than 5 mEq/L, renal insufficiency, 5 units or 10 units of intravenous regular insulin administered in the emergency department, and blood glucose documented within five hours after insulin administration. Of these patients, 133 (19.7%) received 5 units of insulin and 542 (80.3%) received 10 units of insulin.

Measurements and results: The primary outcome was incidence of hypoglycemia (blood glucose less than 70 mg/dl). Secondary outcomes were incidence of severe hypoglycemia (blood glucose less than 40 mg/dl) and change in serum potassium after insulin therapy. Hypoglycemia occurred in 26 of 133 patients receiving 5 units of insulin (19.5%) and in 155 of 542 patients receiving 10 units (28.6%) (difference = -9.1%, 95% confidence interval [CI] -16.8 to -1.3). Severe hypoglycemia occurred in 4 of 133 patients (3.0%) and 37 of 542 patients (6.8%) receiving insulin 5 units and 10 units, respectively (difference = -3.8%, 95% CI -7.4 to 0). Change in serum potassium was similar between groups (-1.0 ± 0.8 mEq/L vs -1.0 ± 0.7 mEq/L, difference = 0, 95% CI -0.1 to 0.1).

Conclusion: In patients with renal insufficiency and hyperkalemia, 5 units of insulin reduced serum potassium to the same extent as 10 units of insulin, but with a lower rate of hypoglycemia. Further controlled studies are needed to confirm these findings.

Hyperkalemia is a frequent and potentially life-threatening complication in patients presenting to the emergency department (ED). Hyperkalemia has been shown to be the cause of 1 in 7 cases of in-hospital cardiac arrest and has been associated with an increased incidence of mortality.[1,2] Management of hyperkalemia typically consists of intravenous insulin and nebulized beta agonists to shift potassium into the intracellular space, intravenous calcium to stabilize cardiac membranes (if electrocardiographic evidence of hyperkalemia exists), and sodium-potassium exchange resins, loop diuretics, or hemodialysis to remove potassium from the body.[1] Dosing of intravenous insulin for hyperkalemia is recommended at 10 units of regular insulin with 25 g to 50 g of intravenous dextrose.[1,3-5] Insulin and dextrose administration has been shown to reduce serum potassium levels by 0.5 mEq/L to 0.9 mEq/L;[6,7] however, some studies suggest that dextrose alone may be sufficient to lower potassium by 0.2 mEq/L to 0.6 mEq/L.[8,9] To date, an ideal insulin regimen that accounts for patient specific characteristics has not been well-defined in the literature.

Renal insufficiency is a major cause of hyperkalemia. In the United States, 13.6% of the population has chronic kidney disease (CKD) and approximately 640,000 patients have end-stage renal disease (ESRD) requiring renal replacement therapy.[10,11] Risk factors for developing hypoglycemia after treatment of hyperkalemia with intravenous insulin include low body weight, renal insufficiency, and no prior history of diabetes.[12-14] Hypoglycemia after intravenous insulin in patients with acute kidney injury (AKI) or ESRD has been reported to occur in 13.1% to 75% of patients, with the largest studies indicating an incidence

of 13.1% to24.6%.[6,12,14] Therefore, defining the proper intravenous insulin dosing regimen to minimize the risk of hypoglycemia in patients with renal insufficiency is warranted.

A drug use evaluation assessing the use of intravenous regular insulin for hyperkalemia treatment conducted at our 664-bed academic medical center revealed that 79% of patients experiencing hypoglycemia had renal insufficiency and 77% were non-diabetic. This finding has prompted many emergency medicine providers at our institution to use a reduced dose of insulin (i.e., 5 units) instead of the more conventionally used insulin dose of 10 units.

The purpose of this study was to determine the safety and efficacy of a reduced dose of insulin for the treatment of hyperkalemia in patients with renal insufficiency. The primary objective of this study was to compare the incidence of hypoglycemia in patients receiving 5 units versus 10 units of insulin

Methods

Study design and patient cohorts

This was a single-center, retrospective cohort study at a large academic medical center with an ED that receives approximately 50,000 to 70,000 patient visits each year. Patients who received intravenous push regular insulin in the ED for the treatment of hyperkalemia were identified through a drug use report in the electronic medical records database from March 1, 2008 through February 29, 2016. Ethics approval was obtained from the local Institutional Review Board.

At the study institution, intravenous push insulin may only be ordered for the treatment of hyperkalemia. Patients were divided into 2 groups based on dose of insulin received (5 units or 10 units). Patients with multiple ED visits were assessed for inclusion by

assignment of random numbers generated within Microsoft Excel to ensure a single ED visit per patient was included.

Inclusion criteria were age 18 years and older, serum potassium greater than 5 mEq/L, renal insufficiency, intravenous regular insulin administered for hyperkalemia in the ED at a dose of 5 units or 10 units, and blood glucose documented within five hours after insulin administration. Renal insufficiency was defined as CKD stages 3 to 5 or AKI stages 1 to 3 according to Kidney Disease: Improving Global Outcomes (KDIGO) classification.[15,16] Exclusion criteria included pregnancy, receipt of dialysis before re-checking the serum potassium level, absence of serum potassium documented before or after insulin therapy, baseline blood glucose less than 70 mg/dl, failure to administer concurrent dextrose with insulin therapy, and administration of additional insulin products for diabetes management before rechecking blood glucose or serum potassium concentrations. Excluded patients were eligible to be reassessed for inclusion if they had additional ED visits during the study time frame.

Methods and measurements

Electronic medical records were used to obtain clinical data. Variables evaluated were age, gender, weight, history of non–insulin-dependent or insulin-dependent diabetes, CKD stage (I or II, III, IV, and V), AKI stage (I, II, and III), length of stay (hospital and intensive care unit), drugs used prior to admission that may have affected blood glucose or serum potassium, drugs commonly administered for treatment of hyperkalemia (dextrose, sodium polystyrene sulfonate, intravenous sodium bicarbonate, intravenous calcium, inhaled albuterol, and intravenous furosemide), and concomitant administration of intravenous drugs containing a dextrose diluent (continuous infusion or piggyback). Creatinine clearance was calculated from the baseline serum creatinine using the Cockcroft-Gault equation. Baseline

serum creatinine was defined as the average of the 3 most recent values available, excluding values from the index admission. AKI stage was determined by comparing the serum creatinine at admission with the baseline serum creatinine. The hyperkalemia protocol at the study institution states intravenous regular insulin is to be given with dextrose 25 g, followed by an additional 25 g of dextrose 1 hour later; a third 25 g dose is to be administered 3 hours after insulin administration if the blood glucose is less than 70 mg/dl. Dextrose may be given by the oral or intravenous route and is determined by the ordering provider. Blood glucose is then checked every 1 hour for 4 occurrences, and the serum potassium is rechecked 2 hours after insulin administration.

Data abstraction was completed by unblinded study investigators. All blood glucose measurements within 5 hours of insulin administration were evaluated, and laboratory and point-of-care values were used. Serum potassium measurements were collected at the time point closest to insulin administration. Drugs commonly administered for treatment of hyperkalemia were collected up to the time point of a postinsulin administration serum potassium measurement. A record of concomitant drugs containing a dextrose diluent was collected up to 5 hours postinsulin administration.

Study outcomes

The primary outcome of the study was the incidence of hypoglycemia (blood glucose less than 70 mg/dl) within 5 hours after insulin administration. Secondary outcomes were the incidence of severe hypoglycemia (blood glucose less than 40 mg/dl) within 5 hours after insulin administration and change in serum potassium, measured as the difference between potassium measured before insulin administration and the first recheck after insulin administration. The independent variable was intravenous regular insulin administered in the ED at a dose of 5 units or 10 units.

Statistical analysis

Analyses were performed on Statistical Package for the Social Sciences (SPSS, Inc., Armonk, NY), version 22.0. Sample size was based on assumptions of an incidence of hypoglycemia of 20% in patients treated with 10 units of insulin and 10% in patients treated with 5 units of insulin. It was estimated that 656 patients would be needed assuming an approximate 1:4 distribution in the 5 unit versus 10 unit group (131 patients in the 5 unit group and 525 patients in the 10 unit group) to achieve 80% power. The data were analyzed using descriptive and univariate analyses. Nominal and continuous data were analyzed using χ^2 and Student *t* test, respectively. Nonparametric data were analyzed using the Mann-Whitney U test.

Results

We identified 1746 orders for intravenous regular insulin in the ED during the selected time period. Of these orders, 1544 were administered as 5 unit or 10 unit doses (Figure 1). After excluding patients with multiple ED visits, 1050 unique patients were available for inclusion. A total of 375 patients were excluded, primarily because of receipt of dialysis (n = 116 [30.9%]) or absence of blood glucose documentation (n = 57 [15.2%]). A total of 675 patients were included in the analysis, 133 (19.7%) in the 5 unit group and 542 (80.3%) in the 10 unit group. Patient demographics were statistically similar, except that the 5 unit insulin group had a greater proportion of male patients compared with the 10 unit group (86 of 133 patients [64.7%] vs 272 of 542 patients [50.2%]) and had a higher incidence of dependence on dialysis (51.1% vs 34.9%) (Table 1). In contrast, the 5 unit insulin group exhibited a significantly lower mean baseline blood glucose compared with the 10 unit group (124.1 ± 47.8 mg/dl vs 137.5 ± 76.6 mg/dl).

Prior to admission, use of drugs affecting blood glucose and serum potassium was balanced between groups (Table 2). Mean total dextrose administered was 5.5 g higher in the 10 unit group (33.6 ± 15.1 g vs 39.1 ± 17.1 g). Other drugs administered for the treatment of hyperkalemia were similar between groups. The most frequent dose of intravenous sodium bicarbonate was 50 mEq (range, 25 mEq to 150 mEq), administered to 97 (87%) patients who received intravenous sodium bicarbonate. Of patients who received sodium polystyrene sulfonate, 443 (79.8%) received a dose of 30 g (range, 15 g to 60 g). Intravenous calcium was most commonly administered at a dose of 1 g calcium gluconate. Of patients who received inhaled albuterol, 125 (59.2%) received a dose of 5 mg (range, 2.5 mg to 20 mg). Lastly, the most frequent dose of intravenous furosemide was 40 mg (range, 20 mg to 80 mg), administered to 45 (50%) patients.

The primary outcome, incidence of hypoglycemia after insulin administration, significantly differed between groups and occurred in 26 of 133 patients (19.5%) in the 5 unit group and 155 of 542 patients (28.6%) in the 10 unit group (difference = -9.1%, 95% confidence interval [CI] -16.8% to -1.3%; Figure 2). Severe hypoglycemia episodes occurred in 4 of 133 patients (3.0%) in the 5 unit group and 37 of 542 patients (6.8%) in the 10 unit group, a difference of -3.8% (95% CI -7.4% to 0%). Change in serum potassium was -1.0 ± 0.8 mEq/L and -1.0 ± 0.7 mEq/L in the 5 unit and 10 unit group, respectively (difference = 0, 95% CI -0.1 to 0.1 mEq/L; Figure 3). Both groups had similar baseline serum potassium (6.4 ± 0.6 mEq/L in the 5 unit group and 6.4 ± 0.7 mEq/L in the 10 unit group; difference = 0, 95% CI -0.1 to 0.1 mEq/L) and postinsulin administration serum potassium levels (5.4 ± 0.7 mEq/L in the 5 unit group and 5.4 ± 0.8 mEq/L in the 10 unit group; difference = 0, 95% CI -0.2 to 0.1 mEq/L). Patients in the 5 unit and 10 unit groups experienced a similar incidence of baseline serum potassium hemolysis (9.0% vs 5.9%) and postinsulin serum potassium hemolysis (6.0% vs 7.2%).

Discussion

In this study, we investigated the safety and efficacy of a reduced dose of insulin for the treatment of hyperkalemia in patients with renal insufficiency. We report a higher incidence of hypoglycemia with 10 units of insulin than with 5 units. Despite use of a lower dose of insulin, the magnitude of potassium decrease was not significantly different from use of a higher insulin dose. To date, this is the largest study to analyze the use of insulin for hyperkalemia and to compare the safety and efficacy of 5 units versus 10 units of insulin.

Insulin dosing for hyperkalemia is recommended as 10 units of intravenous regular insulin by the National Kidney Foundation, the United Kingdom Renal Association, and the American Heart Association.[1,3,5] However, trials investigating insulin treatment for hyperkalemia used doses ranging from 4 units to 20 units, as well as infusions at a rate of 5 milliunits/kg/min for 1 hour.[6,7,12-14,17] One recently published retrospective study compared 5 units and 10 units of intravenous regular insulin for hyperkalemia treatment in 149 patients with low eGFR.[18] This study reported nonsignificant findings of a 15% lower incidence of hypoglycemia for all patients and a 31.5% lower incidence in patients with ESRD with the lower dose of insulin. In comparison, we found a 31.8% lower incidence of hypoglycemia with the lower insulin dose, a finding that was statistically significant. Furthermore, the results are clinically relevant when evaluated in the context of literature showing an association between hypoglycemia and increased mortality.[19-21] Patients who are hypoglycemic (blood glucose less than 72 mg/dl) on admission have an in-hospital mortality rate ranging from 13% to 27% (a 2.5-fold increase compared to patients with blood glucose greater than 72 mg/dl).[20] Furthermore, even patients with mild hypoglycemia (60 mg/dl to 80 mg/dl) are at increased risk of mortality compared with patients with normal glucose values.[21]

The guideline recommended dose of dextrose administered in conjunction with intravenous insulin for hyperkalemia ranges from 25 g to 50 g.[1,3,5] The dextrose protocol at

our institution (dextrose 25 g followed by an additional 25 g of dextrose one hour later) is consistent with this recommendation, but differs in that the total dose of dextrose is administered in divided doses. Moreover, although the average dose of dextrose ranged from 34 g to 39 g per patient in our study, suggesting nonadherence to the institutional protocol, the doses administered were still within the recommended dosing range.

Renal insufficiency is a common risk factor for hypoglycemia events in hospitalized patients, and is present in 50% to 80% of patients with hypoglycemia.[12,19] Proposed mechanisms of hypoglycemia in renal insufficiency include decreased renal clearance of exogenous insulin,[19] impaired glycogenolysis because of uremia,[22] and impaired gluconeogenesis because of removal of substrates during hemodialysis.[23-26] Despite a higher proportion of hemodialysis-dependent patients and a lower baseline blood glucose in the 5 unit insulin group, we found a lower incidence of hypoglycemia with the lower dose. As a result, we propose that a lower insulin dose (i.e., 5 units) may decrease the incidence of hypoglycemia in patients with renal insufficiency, even if other risk factors for hypoglycemia are present.

Our results suggest that an insulin dose of 5 units versus the standard 10 units may be sufficient to lower serum potassium levels in patients with hyperkalemia, when used in combination with other pharmacologic management options. The potassium change in this study is consistent with published literature utilizing insulin for the treatment of hyperkalemia, in which the mean decrease in potassium when combining 5 units or 10 units of insulin with other modalities for hyperkalemia was 1.1 mEq/L.[18]

Our study has several limitations. The retrospective design of the study may have increased the selection bias toward patients with lower baseline blood glucose. Serum potassium was collected at the time point closest to insulin administration, and patients with missing data (serum potassium or blood glucose) were excluded. Although treatment options

for hyperkalemia were similar between groups, the treatments may have been administered in varying order. Furthermore, disease-specific factors affecting blood glucose or serum potassium such as liver disease, malnutrition, and infection were not accounted for. However, the large sample size and similar probability of occurrence of disease-specific factors between groups reasonably negated this potential confounder. An additional limitation is the focus of this study on surrogate measures, such as blood glucose and potassium, rather than clinical outcomes. Although low blood glucose is a well-known, avoidable risk factor in patients being treated with insulin, it is possible that patients experienced asymptomatic hypoglycemia. Furthermore, clinical outcomes associated with hyperkalemia, such as cardiac arrest, were not evaluated. Other limitations of our study relate to the nature of obtaining laboratory values and documentation. We prioritized collection of nonhemolyzed laboratory values, but we did not exclude patients with hemolyzed serum potassium values. Although the laboratory at our institution does not report grossly hemolyzed serum potassium values, mild to moderately hemolyzed potassium results were included in this study. Despite hemolysis, all patients received insulin treatment at the provider's discretion based on available laboratory results. Next, we assumed point-of-care blood glucose and the blood glucose from a basic metabolic panel to be accurate because point-of-care glucometers are calibrated daily. Finally, the 10 unit insulin group received a higher mean total amount of dextrose, which was likely to prevent and treat hypoglycemia.

Given the results of this study, future directions would be to conduct a prospective trial to evaluate the place in therapy of a reduced dose of insulin for hyperkalemia in hemodialysis-dependent patients. A prospective trial may confirm our hypothesis that a reduced dose of insulin results in a lower incidence of hypoglycemia without compromising clinical outcomes. A future trial could evaluate clinical outcomes as well as the time to potassium reduction, two factors that we were unable to assess.

Conclusion

A dose of 5 units of intravenous regular insulin is associated with a lower incidence of hypoglycemia than 10 units of insulin without compromising serum potassium reduction when used to treat hyperkalemia in patients with renal insufficiency. Further controlled studies are needed to confirm these findings.

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Table 1. Patient characteristics.

Characteristic	**5 units insulin (n=133)**	**10 units insulin (n=542)**	**Difference (95% CI)**
Age (years), mean ± SD	59.6 ± 17.6	62.3 ± 16.2	-2.7 (-6.0 to 0.6)
Male, n (%)	86 (64.7)	272 (50.2)	14.5 (5.3 to 23.6)
ABW (kg), mean ± SD	80.9 ± 22.5	80.9 ± 23.7	0 (-4.5 to 4.5)
BMI (kg/m^2), mean ± SD	28.1 ± 7.6	28.6 ± 8.1	-0.5 (-2.0 to 1.0)
Diabetic, n (%)	57 (42.9)	266 (49.1)	-6.2 (-15.6 to 3.2)
Insulin-dependent, n (%)	31 (23.3)	138 (25.5)	-2.2 (-10.2 to 5.9)
Baseline blood glucose (mg/dl), mean ± SD	124.1 ± 47.8	137.5 ± 76.6	-13.5 (-23.9 to -3.0)
CKD stage, n (%)			
I or II	19 (14.3)	88 (16.2)	-2.0 (-8.7 to 4.8)
III	26 (19.5)	151 (27.9)	-8.3 (-16.0 to -0.6)
IV	17 (12.8)	88 (16.2)	-3.5 (-9.9 to 3.0)
V	71 (53.4)	215 (39.7)	13.7 (4.3 to 23.1)
Hemodialysis-dependent, n (%)	68 (51.1)	189 (34.9)	16.2 (6.9 to 25.7)
AKI stage, n (%)	(n=59)	(n=290)	
I	26 (44.1)	135 (46.6)	-2.5 (-16.4 to 11.4)
II	15 (25.4)	59 (20.3)	5.1 (-7.0 to 17.1)
III	18 (30.5)	96 (33.1)	-2.4 (-15.5 to 10.3)
Time to postinsulin serum potassium (hours), median (IQR)	3.2 (2.1, 5.0)	2.8 (2.0, 5.2)	0.4 (-0.3 to 0.4)
Length of stay (days), median (IQR)			
Hospital	3.0 (1.8, 5.0)	3.2 (1.9, 6.4)	-0.2 (-0.9 to 0.1)
Intensive care unit	1.7 (1.3, 2.7)	1.9 (1.0, 3.4)	-0.2 (-0.4 to 0.4)
In-hospital mortality, n (%)	4 (3.0)	18 (3.3)	-0.3 (-3.6 to 3.0)

ABW = actual body weight; AKI = acute kidney injury; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; IQR = interquartile range; SD = standard deviation.

Table 2. Concomitantly administered drugs.

Drugs	5 units insulin (n=133)	10 units insulin (n=542)	Difference (95% CI)
Administered prior to admission			
Drugs causing hyperglycemia, n (%)			
Glucocorticoids	13 (9.8)	62 (11.4)	-1.6 (-7.4 to 4.1)
Drugs causing hypoglycemia, n (%)	15 (11.3)	56 (10.3)	-1.0 (-5.0 to 6.9)
Biguanides	5 (3.8)	27 (5.0)	-1.2 (-4.9 to 2.5)
Sulfonylureas	9 (6.8)	33 (6.1)	0.7 (-4.0 to 5.4)
Thiazolidinediones	3 (2.3)	8 (1.5)	0.8 (-2.0 to 3.5)
Drugs causing hyperkalemia, n (%)	57 (42.9)	219 (40.4)	2.5 (-6.9 to 11.8)
ACE inhibitors	40 (30.1)	130 (24.0)	6.1 (-2.5 to 14.7)
Angiotensin receptor blockers	12 (9.0)	63 (11.6)	-2.6 (-8.2 to 3.0)
Potassium supplements	5 (3.8)	21 (3.9)	-0.1 (-3.7 to 3.5)
Potassium sparing diuretics	15 (11.3)	49 (9.0)	2.3 (-3.7 to 8.1)
Drugs causing hypokalemia, n (%)	31 (23.3)	152 (28.0)	-4.7 (-12.9 to 3.4)
Thiazide-type diuretics	8 (6.0)	32 (5.9)	0.1 (-4.4 to 4.6)
Loop diuretics	27 (20.3)	130 (24.0)	-3.7 (-11.4 to 4.0)
Administered for treatment of hyperkalemia			
Dextrose (g), mean ± SD	33.6 ± 15.1	39.1 ± 17.1	-5.5 (-8.4 to -2.5)
Sodium polystyrene sulfonate, n (%)	104 (78.2)	451 (83.2)	-5.0 (-12.7 to 2.7)
I.V. sodium bicarbonate, n (%)	18 (13.5)	94 (17.3)	-3.8 (-10.4 to 2.8)
I.V. calcium gluconate, n (%)	55 (41.4)	272 (50.2)	-8.8 (-18.2 to 0.5)
Inhaled albuterol, n (%)	49 (36.8)	164 (30.3)	6.5 (-2.5 to 15.7)
I.V. furosemide, n (%)	18 (13.5)	72 (13.3)	-0.2 (-6.2 to 6.7)
I.V. drugs containing dextrose diluent, n (%)			
Continuous infusion	6 (4.5)	32 (5.9)	-1.4 (-5.4 to 2.7)
Piggyback	10 (7.5)	63 (11.6)	-4.1 (-9.3 to 1.1)

ACE = angiotensin converting enzyme; CI = confidence interval; I.V. = intravenous; SD = standard deviation.

Figure legends

Figure 1. Patient flow diagram of study cohort and excluded patients. BG = blood glucose; ED = emergency department; IV = intravenous.

Figure 2. Incidence of hypoglycemia and severe hypoglycemia. The primary outcome was incidence of hypoglycemia (blood glucose less than 70 mg/dl). Incidence of severe hypoglycemia (blood glucose less than 40 mg/dl) was a secondary outcome.

Figure 3. Mean baseline and postinsulin serum potassium levels. Change in serum potassium after insulin therapy was a secondary outcome. Error bars represent 1 standard deviation.