Hypoglycemia Associated With Insulin Use During Treatment of Hyperkalemia Among Emergency Department Patients

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Abstract

Purpose: Hypoglycemia is a common adverse event associated with insulin during treatment of hyperkalemia in hospitalized patients; however, limited data exist regarding hypoglycemia incidence and appropriate dosing strategies for treatment of patients in the emergency department. The study objective was to determine the incidence of hypoglycemia associated with insulin use during treatment of hyperkalemia among patients seen in the emergency department. **Methods:** This was an Institutional Review Board (IRB)–approved retrospective, chart-review study. All adult patients who received intravenous regular insulin as a result of an order from the emergency department hyperkalemia order set were eligible for inclusion. The main clinical outcomes were incidence of hypoglycemia (blood glucose <70 mg/dL) and severe hypoglycemia (blood glucose <40 mg/dL). Blood glucose was checked within 24 hours of insulin administration. **Results:** A total of 172 patients were included. The incidence of hypoglycemia was 19.8% (n = 34) and the incidence of severe hypoglycemia was 5.2% (n = 9). Hypoglycemic patients had a significantly lower median blood glucose at baseline compared to those who did not develop hypoglycemia (83.5 [72.0–112.0] mg/dL vs 123.0 [96.0–167.0] mg/dL, $P < .0001$); however, no difference was noted between groups in the average insulin dose administered (0.11 ± 0.04 units/kg vs 0.12 ± 0.05 units/kg, $P = .6175$). **Conclusion:** There is a concerning risk of hypoglycemia associated with insulin use during treatment of hyperkalemia in the emergency department. Standard insulin doses may not be appropriate in some cases like patients with lower baseline blood glucose. Further research is warranted to develop safer hyperkalemia treatment protocols that mitigate this high risk of hypoglycemia associated with insulin use.

Keywords

hypoglycemia, insulin, hyperkalemia, emergency department

Introduction

Hyperkalemia is a common electrolyte disorder that can cause clinically significant adverse outcomes including cardiac arrhythmia leading to death.¹ A variety of factors including renal insufficiency, aldosterone insufficiency, and medication use have been associated with an increased risk of hyperkalemia.^{2,3} In 2014, approximately 141 million patients visited emergency departments in the United States.⁴ Epidemiological studies estimate that 2.6% to 3.5% of emergency department visits and the resulting hospital admissions arise from hyperkalemia; however, these figures may underestimate the problem.⁵ Clinicians initiate treatments for hyperkalemia based on varying serum potassium thresholds and certainly when patients display serious signs and symptoms associated with hyperkalemia including abnormal electrocardiographic changes. Treatment options include protection of myocardial tissue with intravenously

administered calcium, promotion of intra-cellular shifting of potassium with insulin, albuterol, or sodium bicarbonate in the setting of metabolic acidosis, and removal of potassium from the body with ion-exchange agents, loop diuretics, or hemodialysis.^{2,6} Intravenously administered regular insulin is a commonly used early treatment. The primary adverse event associated with insulin in this setting is hypoglycemia, which is particularly concerning given the evidence linking hypoglycemia to poor clinical outcomes.^{7–10}

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Several studies have evaluated the incidence of hypoglycemia among patients who have received hyperkalemia treatment with insulin; however, many of these studies have been limited by methodological challenges including small sample size.¹¹ Some studies have specifically focused on patients with underlying renal insufficiency since insulin is dependent on adequate kidney function for clearance from the body.¹²⁻¹⁴ The range of insulin doses used in clinical practice for treatment of hyperkalemia varies; however, most institutions typically use 10 units of regular insulin administered intravenously along with 25 to 50 g of dextrose.¹¹ In a retrospective study, Schafers and colleagues looked at all hospitalized patients regardless of underlying renal function who received treatment with insulin for hyperkalemia and found that 8.7% experienced hypoglycemia (blood glucose <70 mg/dL) and 2.3% experienced severe hypoglycemia (blood glucose level <40 mg/dL).¹⁵ Nearly all patients who developed posttreatment hypoglycemia (95%) received concomitant dextrose with insulin. In a follow-up to this study, investigators found that a weight-based insulin dosing protocol (0.1 unit/kg) for hyperkalemia treatment among hospitalized patients was associated with a lower incidence of hypoglycemia when compared to patients who received the standard 10 unit dose of insulin, although this difference was not statistically significant (10.6% vs 19.7%, $P = .22$).¹⁶

Treatment of patients with hyperkalemia using insulin is common in the emergency department; however, limited data exist regarding the incidence of hypoglycemia associated with insulin treatment of hyperkalemia specifically in this setting. The objective of this study was to evaluate the incidence of hypoglycemia in patients who were treated for hyperkalemia with regular insulin while receiving medical care in the emergency department.

Methods

This was a retrospective, electronic medical chart review of patients at 2 separate emergency departments associated with a community hospital system from January 1, 2016 to June 30, 2016. The emergency departments are located in a community hospital health system found in a large metropolitan area of the United States with annual patient visits numbering approximately 140 000. An emergency department hyperkalemia treatment order set has been integrated into the computerized physician order entry system at the institution since 2009. Prescribers are encouraged to use the order set when ordering medications to treat patients presenting to the emergency department with hyperkalemia (normal serum potassium range defined as 3.6-5.1 mmol/L). All adult patients who were seen in the emergency department and who received at least one dose of intravenous regular insulin ordered from the emergency department hyperkalemia treatment order set were eligible for inclusion in the study, therefore no sample size was calculated. The electronic pharmacy system, which is integrated into the electronic medical chart,

was used to identify orders for intravenous regular insulin that were generated specifically from the emergency department hyperkalemia treatment order set during the specified study period. Treatments available from this order set included preset single-dose orders for intravenous calcium chloride or gluconate 1 g, nebulized albuterol sulfate 5 mg, intravenous sodium bicarbonate 8.4% 50 mEq, oral or rectal sodium polystyrene sulfonate 60 g, and intravenous regular insulin 10 units. Administration of 25 g of dextrose with intravenous regular insulin is part of the order set; however, physicians were able to adjust the dose of insulin and/or grams of dextrose administered based on clinical judgment. The order set does not include a specified follow-up time for checking blood glucose after insulin administration. Physicians and nurses were able to order posttreatment finger stick blood glucose measurements based on clinical judgment and observation of the patient. Serum potassium was measured using a regular serum blood draw. Patients who did not have posttreatment serum potassium or capillary finger stick blood glucose were excluded from the study. In addition, pediatric patients (age <18 years) were ineligible for inclusion in the study. Informed consent was not obtained since the study involved observation of usual care. The Institutional Review Boards from the investigators' institution and the study site approved the study protocol. This study was conducted in accordance with accepted ethical standards of research.

Baseline demographics included age, gender, weight, electrocardiographic changes, hospitalization, admission diagnosis, and past medical history of diabetes mellitus, chronic kidney disease including use of dialysis, prior hyperkalemia, and prior hypoglycemia. History of hyperkalemia or hypoglycemia was determined by examining records of prior visits to the emergency department or hospital admissions at the study institution. Laboratory parameters that were collected at baseline included serum potassium, magnesium, creatinine, and blood glucose. Estimated creatinine clearance was calculated using the Cockcroft-Gault formula. Additional clinical parameters that were collected included treatments used for hyperkalemia, insulin dose in units, grams of dextrose used, posttreatment serum potassium, posttreatment capillary finger stick blood glucose, and time to posttreatment capillary finger stick blood glucose measurement. Posttreatment blood glucose measurements were obtained by reviewing the first documented capillary finger stick reading within 24 hours of intravenous regular insulin administration recorded in the electronic medical chart by nurses as part of their usual practice. An interval of 24 hours was used for follow-up since the current order set included no prespecified direction to physicians and nurses on the timing of follow-up blood glucose measurement and therefore investigators wanted to determine the average time from treatment to blood glucose measurement. Physicians or nurses ordered posttreatment capillary blood glucose measurements based on clinical judgment and observation of the patient. Time to posttreatment capillary

Table 1. Patient Demographics.

Parameter	Total sample treated for hyperkalemia (n = 172) ^a	Posttreatment blood glucose groups ^b	
		BG ≥ 70 mg/dL (n = 138)	BG <70 mg/dL (n = 34)
Mean $\pm$ SD, age, y	65.0 $\pm$ 18.9	65.5 $\pm$ 19.6	63.1 $\pm$ 16.1
Female (%)	52	51	53
Mean $\pm$ SD CrCl, mL/min	14.3 $\pm$ 16.0	14.2 $\pm$ 16.1	14.9 $\pm$ 15.5
BMI ^a	28.4 $\pm$ 9.1	27.7 $\pm$ 8.3	31.1 $\pm$ 11.5
Past medical history (%)			
Diabetes	53	51	59
CKD nondialysis	31	30	41
Hemodialysis	46	47	41
Hyperkalemia ^c	24	25	24
Hypoglycemia ^c	9	12	0

Note. BG = blood glucose; BMI = body mass index; CKD = chronic kidney disease; SD = standard deviation.

^aEligible patients received regular insulin as an order from the emergency department hyperkalemia treatment order set during the study period.

^bAfter treatment with regular insulin from emergency department hyperkalemia treatment order set, patients were divided into groups based on their posttreatment capillary blood glucose reading of either blood glucose ≥ 70 mg/dL (n = 138) or blood glucose <70 mg/dL (n = 34).

^cHistory of these conditions was based on review of prior admissions and visits to the study institution.

finger stick blood glucose was determined by comparing the time for the initial insulin administration to the time when the first postinsulin treatment finger stick blood glucose was recorded. The electronic medication administration record was reviewed to obtain doses and time of administration for insulin and dextrose.

The main clinical outcomes of interest were the percentage of patients with hypoglycemia (blood glucose <70 mg/dL) and the percentage of patients with severe hypoglycemia (blood glucose <40 mg/dL) after receiving treatment with intravenous regular insulin for treatment of hyperkalemia. The definition of severe hypoglycemia as blood glucose less than 40 mg/dL was chosen for ease of comparison to prior studies of insulin treatment for hyperkalemia.¹⁴⁻¹⁶ Additional clinical endpoints of interest that were evaluated included the average blood glucose after treatment, average insulin dose in units per patient's weight in kilograms, relationship of hypoglycemic events to time, change in serum potassium after treatment, and percentage of patients that achieved a serum potassium level less than 5.0 mmol/L. Furthermore, selected clinical endpoints were compared between patients with posttreatment blood glucose less than 70 mg/dL (hypoglycemia) and posttreatment blood glucose ≥ 70 mg/dL (normal).

Descriptive statistics was used to summarize the demographics and the proportion of patients with hypoglycemia. For subgroup analyses involving categorical variables such as comparing patients who had hypoglycemia with those who did not, chi-square or Fisher's Exact test was used. Where the categories were 3 or more, analysis of variance (ANOVA) was used. Similarly Student *t* test was used for continuous variables such as age. Associations between dependent variables, such as posttreatment hypoglycemia,

and specific independent variables, such as insulin dose, were estimated using multiple regressions while controlling for demographics. SAS software, version 9.3 (SAS Inc. Cary, NC), was used for the analysis. A *P* value of less than .05 was considered statistically significant.

Results

A total of 187 patients received intravenous regular insulin from the emergency department hyperkalemia treatment order set during the 6 month period. Fifteen patients were excluded from the study for missing data including not having a follow-up serum potassium or capillary finger stick blood glucose after treatment with insulin, which resulted in a total of 172 patients being included in the final analysis. As noted in Table 1, the average age of patients in the study was 65 $\pm$ 18.9 years with 52% being female and a significant majority having a history of chronic kidney disease (77%). Most patients in the study had electrocardiographic changes in the emergency department (80%) and a large number of patients required hospital admission (84%) with approximately half of these admissions related to hyperkalemia. Several concurrent treatments for hyperkalemia were utilized in the emergency department including calcium (80%), sodium bicarbonate (72%), albuterol (72%), and sodium polystyrene sulfonate (66%). Nearly three-quarters of the patients received 10 units of regular insulin (72%), while the remainder received doses less than 10 units. Furthermore, the vast majority of patients received 25 g of dextrose along with regular insulin (92%); however, 10 patients received no dextrose and 3 patients received 50 g of dextrose.

The incidence of hypoglycemia in this study was 19.8% (n = 34) and the incidence of severe hypoglycemia was

Table 2. Clinical Endpoints.

Parameter	Total sample treated for hyperkalemia (n = 172) ^a	Posttreatment blood glucose groups ^b	
		BG $\geq$ 70 mg/dL (n = 138)	BG <70 mg/dL (n = 34)
Mean $\pm$ SD baseline BG, mg/dL ^c	143.3 $\pm$ 115.0	154.2 $\pm$ 123.0	99.3 $\pm$ 56.6
Median (interquartile range) baseline BG, mg/dL ^c	112.0 (88.5 – 156.0)	123.0 (96.0-167.0)	83.5 (72.0-112.0)
Mean $\pm$ SD posttreatment BG, mg/dL ^c	113.2 $\pm$ 66.2	129.1 $\pm$ 64.3	48.4 $\pm$ 14.1
Median (interquartile range) posttreatment BG, mg/dL	100.5 (76.5-127.5)	111.0 (92.0-137.0)	50.0 (38.0-61.0)
Treated with insulin 10 units (%)	72	69	82
Mean $\pm$ SD insulin dose, units/kg	0.12 $\pm$ 0.05	0.12 $\pm$ 0.05	0.11 $\pm$ 0.04
Mean time to first BG measurement, (hr)	6.7	7.3	4.4
Mean $\pm$ SD baseline serum K, mmol/L ^c	6.3 $\pm$ 0.89	6.2 $\pm$ 0.8	6.6 $\pm$ 0.8
Mean $\pm$ SD posttreatment serum K, mmol/L	4.7 $\pm$ 0.7	4.7 $\pm$ 0.7	4.9 $\pm$ 0.6
Mean $\pm$ SD change in serum K, mmol/L	1.7 $\pm$ 1.2	1.6 $\pm$ 1.1	2.1 $\pm$ 1.6
Posttreatment serum K <5.0 mmol/L (%)	70	70	68

Note. BG = blood glucose; K = potassium; SD = standard deviation.

^aEligible patients received regular insulin ordered from the emergency department hyperkalemia treatment order set during the study period.

^bAfter treatment with regular insulin from emergency department hyperkalemia treatment order set, patients were divided into groups based on their posttreatment capillary blood glucose readings of blood glucose $\geq$ 70 mg/dL (n = 138) or blood glucose <70 mg/dL (n = 34).

^c $P < 0.05$ for comparison between patients with posttreatment blood glucose $\geq$ 70 mg/dL (n = 138) versus posttreatment blood glucose <70 mg/dL (n = 34).

5.2% (n = 9). Most cases of hypoglycemia (71%, n = 24) were identified within 6 hours of insulin administration. As noted in Table 2, patients who developed hypoglycemia had a significantly lower median serum blood glucose level at baseline compared to those with posttreatment blood glucose $\geq$ 70 mg/dL (83.5 [72.0-112.0] mg/dL vs 123.0 [96.0-167.0] mg/dL, $P < .0001$); however, no differences were noted between these groups with respect to the average insulin dose administered (0.11 $\pm$ 0.04 units/kg vs 0.12 $\pm$ 0.05 units/kg, $P = .6175$) or the percentage of patients that received 10 units of insulin as opposed to a lower dose (82% vs 69%, $P = .1405$). Posttreatment hypoglycemia was significantly associated with baseline blood glucose ($P = .0083$), while no association was noted with average insulin dose ($P = .0594$). Hypoglycemic patients were less likely to have had a prior history of hypoglycemia than those who had normal posttreatment blood glucose after insulin treatment (0% vs 12%, $P = .0439$). There was no increased risk for hypoglycemia associated with prior history of diabetes, chronic kidney disease not requiring dialysis, or hemodialysis. Furthermore, no significant differences were observed between patients who developed hypoglycemia and those who did not develop hypoglycemia with respect to the average decrease in serum potassium after insulin treatment (2.1 $\pm$ 1.6 vs 1.6 $\pm$ 1.1 mmol/L) or the percentage of patients that achieved a posttreatment serum potassium level in the normal range (68% vs 70%).

Discussion

This is among the first studies to evaluate the incidence of hypoglycemia specifically among patients in the emergency department who received intravenous regular insulin for the

treatment of hyperkalemia. Insulin treatment was found to be effective in most patients; however, a relatively large number of patients also experienced posttreatment hypoglycemia, including patients who had blood glucose levels well below thresholds noted for cognitive impairment and cerebral compromise. This may be a significant finding of concern for clinicians and health systems who strive to promote an environment in the emergency department that optimizes patient safety outcomes. The public health implications could be substantial given the approximate 41.9 visits to the emergency department each year for every 100 persons living in the United States.⁴ Furthermore, almost 1 in every 10 visits to the emergency department leads to hospital admission. Insulin is well known to be a high-risk medication.¹⁷⁻²⁰ Accreditation standards make it imperative that hospitals develop policies and procedures that promote the safe use of insulin throughout the institutional setting.²¹ There are a number of factors that may contribute to patient sensitivity to insulin in the emergency department including the ubiquity of chronic kidney disease in the general population, widespread use of medications with potential to cause acute kidney injury such as nonsteroidal antiinflammatory drugs, and lack of standardization with respect to insulin dosing for hyperkalemia treatment.

Hypoglycemia is a clinically relevant and widely recognized concern for patients receiving medical care. Published studies show a wide range of hypoglycemia rates associated with the use of insulin for treatment of hyperkalemia.¹¹ The incidence of inpatient hypoglycemia has been reported to be 8.7% to 19.7%.^{12,13,15} Schafers and colleagues looked at 219 hospitalized patients with an average age of 56 years and reported that 8.7% of patients who received insulin developed hypoglycemia (blood glucose <70 mg/dL) and 2.3% of

patients developed severe hypoglycemia (blood glucose <40 mg/dL). The current study, which specifically focused on patients in the emergency department, found an incidence of hypoglycemia that was more than double of what was reported by Shafers and colleagues. One key difference between these 2 studies was a much older population on average in the current study with mean age of 65.0 ± 18.9 years. Furthermore, the current study included all patients who received treatment with insulin regardless of baseline serum potassium including if that level was less than 6.0 mEq. Hypoglycemia rates are similar to what has been reported in previous studies of hospitalized, hyperkalemic patients with renal insufficiency.^{12,13} Pierce and colleagues conducted a retrospective evaluation of hospitalized patients with hyperkalemia who received intravenous regular insulin at 2 different doses and found rates of hypoglycemia that were 16.7% (5 units) and 19.7% (10 units), respectively.¹² When looking specifically at dialysis patients, these investigators found extremely high rates of hypoglycemia of 22.6% (5 units) and 33% (10 units). The current study was similar in that a large percentage of patients had a prior history of chronic kidney disease including many who were on dialysis. Insulin requires a high degree of renal clearance for elimination from the body; therefore, it is not surprising that renal dysfunction may be associated with a greater likelihood of developing hypoglycemia. More recently the American Diabetes Association has defined clinically significant hypoglycemia as a blood glucose reading of less than 54 mg/dL, while severe hypoglycemia is noted to be any threshold that causes severe cognitive impairment or requires assistance from others for the patient to recover.²² Based on these definitions, large numbers of patients treated for hyperkalemia in the emergency department with insulin may be at risk for serious, clinically important hypoglycemia. Future work should focus on developing safer and more patient specific guidelines related to treatment of hyperkalemia with insulin, particularly when dealing with patients with renal insufficiency.

Insulin and dextrose dosing may be important considerations to evaluate in developing safer treatment recommendations for hyperkalemia that mitigate the unacceptably high rates of hypoglycemia seen in recent studies. Wheeler and colleagues evaluated the use of a weight-based insulin dosing protocol for treatment of hyperkalemia (0.1 unit/kg) and found a trend toward less hypoglycemia compared to patients who received the standard 10 unit dose.¹⁶ No information was provided regarding the amount of dextrose used, and none of these patients appeared to have been treated in the emergency department. In the current study, most patients received 10 units of insulin; however, the average weight-based insulin dose was comparable between patients who developed hypoglycemia (0.11 ± 0.04 units/kg) and those who had normal posttreatment blood glucose (0.12 ± 0.05 units/kg). Furthermore, average insulin dose did not appear to be substantially different than the weight-based insulin dosing protocol studied by Wheeler and colleagues. A recently published retrospective study of patients with renal

insufficiency treated for hyperkalemia in an academic emergency department found that a lower dose of regular insulin (5 units) was associated with a significantly lower incidence of hypoglycemia compared to the use of 10 units (19.5% vs 28.6%).²³ The average grams of dextrose used in this academic emergency department setting was higher compared to what was observed in our study. Interestingly, the vast majority of patients who had a hypoglycemic event in our study received 25 g of dextrose (88%), while only 2 patients received 50 g of dextrose.

Further research is warranted to better characterize the appropriate dosing for insulin and dextrose in protocols used in the emergency department since nearly 1 in 5 patients are at risk for a serious adverse drug event. The potential clinical and cost implications of hypoglycemia in the emergency department need to be better characterized. Various publications have demonstrated the importance of adopting approaches to care that will decrease the risk of adverse drug reactions for patients being treated in institutional settings.²⁴⁻²⁶ One prior study of inpatients receiving treatment with insulin for hyperkalemia found an association between low pretreatment blood glucose and the risk of developing posttreatment hypoglycemia.¹³ The current study also found that posttreatment hypoglycemic patients had significantly lower baseline blood glucose levels compared to those with normal posttreatment blood glucose levels; however, there were no significant differences in the dose of insulin each group received. A more tailored approach to insulin dosing for hyperkalemia treatment in the emergency department is recommended. This approach should take into consideration baseline blood glucose levels, particularly in patients with renal insufficiency. Furthermore, more rapid blood glucose checks after insulin treatment may be warranted. Emergency departments should prioritize the development of safer, effective protocols and dosing algorithms that take into consideration patient specific factors, such as baseline blood glucose, with the goal of promoting better patient safety outcomes.

There are a number of limitations to this study including the retrospective nature of the design. Furthermore, evaluation was limited to 2 moderately sized emergency departments associated with a single community hospital system. In addition, there was no evaluation of the association between hypoglycemia and potential cases of acute kidney injury. Since outpatient medication histories were not consistently taken, it remains unclear to what extent patients may have been taking medications such as insulin or sulfonylureas prior to presentation that increased hypoglycemia risk. Future research could offer greater diversity with respect to geographic locations and health systems.

Conclusion

This study suggests an association between insulin treatment of hyperkalemia in the emergency department and posttreatment hypoglycemia. Certain insulin doses and grams of dextrose may not be appropriate in select patients such as those

with low baseline blood glucose. Further studies should address developing dosing protocols that take into consideration patient specific factors such as baseline blood glucose to reduce the overall incidence of hypoglycemia observed in emergency department settings.

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