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Original Contribution

# Hypoglycemia as a complication of intravenous insulin to treat hyperkalemia in the emergency department☆

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ABSTRACT

*Introduction:* Complications associated with the emergency department (ED) management of hyperkalemia are not well characterized. The goals of this study were to describe the frequency of hypoglycemia following the use of insulin to shift potassium intracellularly and to examine the association of key variables with this complication.
*Methods:* Adult ED patients (≥18 years old) with hyperkalemia (>5.3 mmol/L) were identified in the electronic medical record over a 5-year period at the study site. Patient characteristics, laboratory results, and treatments in the ED were captured. A generalized estimating equation (GEE) model was utilized to determine independent associations with the development of hypoglycemia.
*Results:* 1307 encounters were identified where hyperkalemia was present. Hypoglycemia (defined as a glucose <70 mg/dL) occurred in 68/409 (17%) of patients given insulin, compared to 4% of patients who did not receive insulin. Lower glucose prior to insulin (adjusted odds ratio [aOR] 0.90; 95% confidence interval [95% CI] 0.85 to 0.96), higher doses of insulin (aOR 1.07; 95% CI 1.01 to 1.15) and lower doses of D50 (aOR 0.98; 95% CI 0.97 to 0.99) were independently associated with hypoglycemia in the multivariate analysis. Age, history of diabetes, and history renal failure were not independently associated.
*Conclusion:* Hypoglycemia is a frequent complication of treatment with IV insulin in the ED. Interventions such as standardized protocols to assist with the ED management of hyperkalemia should be developed; their efficacy and safety should be compared.



## 1. Introduction

Hyperkalemia is an important condition encountered by emergency physicians. Emergency physicians will increasingly encounter hyperkalemia in the emergency department (ED) as the number of patients being treated for end-stage renal disease increases [1]. The presence of hyperkalemia in ED patients is associated with significant morbidity [2]. Hyperkalemia can cause ventricular dysrhythmias, heart block, other cardiac conduction abnormalities, muscle weakness, paralysis, or death. Treatments include the administration of medications to shift potassium intracellularly and provide cardiac stabilization while definitive potassium removal (e.g. dialysis) is arranged.

Intravenous insulin has been demonstrated to temporarily lower the serum potassium in the clinical setting, however the risks associated with this treatment in the emergency setting is not well-characterized [3-5]. Hypoglycemia after insulin administration has been described in chronic dialysis units and inpatient settings, but prior studies have included patients without acute illness, and in some cases, without hyperkalemia [3,6,7]. Furthermore, while previous work has described patient and treatment-related variables in patients that experience hypoglycemia, these descriptions have not included analyses to help determine which variables are most influential [8-11].

The more severe manifestations of hypoglycemia can include cognitive impairment, behavioral abnormalities, seizure, and death [12]. Furthermore, in the setting of concomitant critical illness, even a single episode of severe hypoglycemia has been described to be independently associated with increased mortality [13]. Patients in the emergency department are likely at risk for poor caloric intake due to acute illness and lack of access to food, potentially increasing the risk of hypoglycemia.

We sought to describe the rate of hypoglycemia following the administration of insulin for the treatment of hyperkalemia in the emergency setting and to examine independent associations between key variables and the development of hypoglycemia.

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## 2. Methods

### 2.1. Study design and setting

This is a retrospective observational cohort study conducted in an urban, Level 1 trauma center with approximately 100,000 annual visits. There is a large nephrology practice serving chronic dialysis patients that is based at the study site. A standardized protocol for the treatment of hyperkalemia did not exist at the study site during the period of data collection. This study was approved by the health system's Institutional Review Board.

Adult ED patients (≥18 years old) with hyperkalemia (>5.3 mmol/L, the local laboratory cutoff) between January 2010 and June 2015 were identified in the electronic medical record. Potassium results in which the specimen was noted to be hemolyzed, as documented by laboratory staff in the medical record, were excluded, as these were likely to be erroneous.

### 2.2. Study protocol

A blinded analyst extracted data directly from the medical record without manual chart review, including patient demographics (age, gender, history of end-stage renal disease, history of diabetes), laboratory values (potassium, glucose, and creatinine), and treatments administered in the ED (intravenous insulin, dextrose 50% [D50], loop diuretics, calcium [gluconate or chloride], sodium bicarbonate, nebulized albuterol, or oral sodium polystyrene sulfonate). The time of ED laboratory results and treatments was captured with these data. All variables of interest were screened to ensure there were no implausible values present for any variable. Additionally, 20 randomly selected charts were manually reviewed by two of the investigators (BD and EC) to confirm accuracy of the data extraction. All data points were accurate with the exception of the presence of end-stage renal disease (ESRD), which was not reliably captured by searching for the ICD-9 codes 585.5 or 585.6. All patient charts were then manually reviewed to abstract the presence or absence of ESRD at the time of the encounter.

### 2.3. Outcome measures

Hypoglycemia associated with intravenous insulin treatment was defined as a glucose value <70 mg/dL (the local laboratory cutoff) within 3 h following intravenous insulin administration in the ED. Patients without a glucose value obtained within 3 h after insulin administration were classified as not having experienced hypoglycemia. Three hours was chosen as previous work has demonstrated that hypoglycemia can occur up to 3 h following administration of intravenous insulin [9,14]. As a comparison, we also considered patients who did not receive insulin, and examined the first 3 h of their ED encounter to determine if hypoglycemia was present.

### 2.4. Data analysis

Baseline characteristics and ED management of hyperkalemia in this patient population are described. The primary analysis of hypoglycemia is descriptive: the proportion of encounters in which hypoglycemia occurred is reported, and the mean or median and associated 95% confidence intervals of variables that may influence the development of hypoglycemia (pre-insulin glucose value, insulin and D50 dose) are presented, stratified by whether hypoglycemia occurred.

To determine if any variables were independently associated with the development of hypoglycemia after insulin administration, we created a generalized estimating equation (GEE) model with exchangeable correlation structure. GEE was used instead of multivariable logistic regression because some patients had multiple encounters. The following independent variables were selected a priori, and were chosen because they could plausibly be related to the development of hypoglycemia after ED insulin administration for hyperkalemia: pre-insulin glucose value, insulin dose, D50 dose, age, history of diabetes mellitus, and history of ESRD. History of diabetes mellitus was selected because insulin resistance may influence the development of hypoglycemia; ESRD was selected because insulin is cleared more slowly if ESRD is present [15,16], which may increase the risk of hypoglycemia.

All analyses were conducted using Stata 12.1 (StataCorp, College Station, TX).

## 3. Results

During the study period, 1662 patient encounters were identified; 355 encounters were excluded because of a hemolyzed sample, yielding 1307 patient encounters with 914 unique patients that were included in the analysis. Mean potassium was 6.0 mmol/L [range 5.4–9.4 mmol/L]. Patient demographics, results of ED diagnostic evaluation, and ED treatments are presented in Table 1.

For encounters with hyperkalemia in which insulin was administered, 344/409 (84%) had a glucose value obtained within 3 h following administration of insulin. Hypoglycemia following IV insulin occurred in 68/409 (17%) of encounters. In comparison, patients with hyperkalemia that did not receive IV insulin experienced hypoglycemia within the first 3 h in 35/898 (4%) of encounters.

Severe hypoglycemia, classified as a glucose of <50 mg/dL, was present in 31 (8%) of encounters. Of the 112 patients with a pre-insulin glucose <100 mg/dL (upper limit of the local laboratory reference range), hypoglycemia occurred in 38 (34%). For the 65 patients with no glucose value obtained in the 3 h following insulin administration, 63 had a glucose obtained within 24 h; 11 (17%) had a glucose value below 70 mg/dL in that timeframe. The pre- and post-insulin glucose values for patients who received insulin are displayed in Fig. 1.

Univariate analysis comparing pre-insulin glucose value, insulin dose, and D50 dose for those with and without hypoglycemia are presented in Table 2. Results from the generalized estimating equations for independent associations with hypoglycemia are displayed in Table 3. Lower glucose value prior to insulin, higher insulin dose administered, and lower D50 dose administered were significantly associated with increased odds of developing hypoglycemia.

**Table 1**
Patient characteristics and emergency department treatments.

| | Value |
|---|---|
| Characteristic | |
| Age, mean ± SD, years | 57 ± 16 |
| Male gender – no. (%)[a] | 567 (62) |
| Medical history – no. (%)[a] | |
| Normal renal function | 276 (30) |
| Elevated creatinine | 375 (41) |
| ESRD | 263 (29) |
| Diabetes mellitus | 357 (39) |
| Medications administered – no. (%) | |
| Received any treatment for hyperkalemia in the ED | 816 (62) |
| Calcium chloride or calcium gluconate, IV | 661 (51) |
| Insulin, IV | 409 (31) |
| 50% dextrose, IV | 359 (27) |
| Sodium bicarbonate, IV | 264 (20) |
| Albuterol, nebulized | 203 (16) |
| Loop diuretics, IV | 123 (9) |
| Sodium polystyrene sulfonate, oral | 32 (2) |
| Baseline laboratory values | |
| Pre-insulin glucose value, median (IQR), mg/dL[b] | 131 (98–260) |
| Serum potassium, mean ± SD (range), mmol/L | 6.0 ± 0.7 (5.4–9.4) |

ESRD: end stage renal disease; IV: intravenous; SD: standard deviation.
[a] The denominator for these variables is 914 unique patients.
[b] 368/409 patients had a glucose value obtained prior to insulin administration.

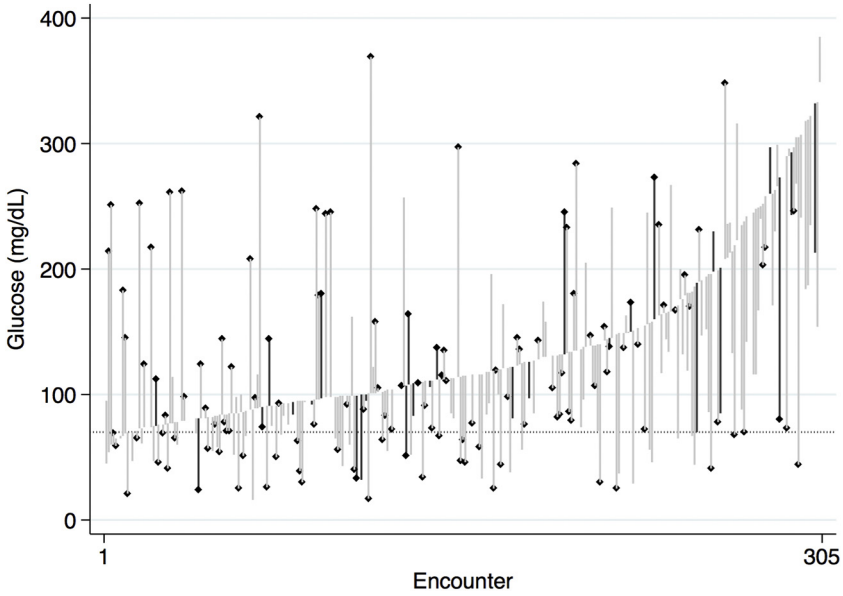


**Fig. 1.** Pre- and post-insulin glucose values for patients that received insulin for treatment of hyperkalemia are shown. The x-axis lists the encounter number, sorted in order of pre-insulin glucose value. The y-axis represents glucose values; each encounter has a single vertical line that connects the pre- to the post-insulin glucose value. Encounters with gray lines received 10 or more units of insulin; those with black lines received 5 units of insulin. Diamonds are placed at the post-insulin glucose value for those that received 50 g of dextrose; if a diamond was not placed the patient received either 0 or 25 g of dextrose. The reference line for hypoglycemia is placed at 70 mg/dL. Patients with a missing pre- or post-glucose value are not displayed; one patient with a missing pre-insulin glucose value developed hypoglycemia with a glucose of 68 mg/dL. For graphical simplicity, patients with a pre- or post-insulin glucose value >400 mg/dL are not pictured in this figure. One patient with a pre-insulin glucose >400 mg/dL developed hypoglycemia, with a post-insulin glucose value of 50 mg/dL.

## 4. Discussion

### *4.1. Significance of main findings*

This study reports on the rate of hypoglycemia following insulin treatment for hyperkalemia in the ED setting and describes which variables were independently associated with this outcome. The administration of intravenous insulin in this setting is a mainstay in the treatment for hyperkalemia, yet like virtually every treatment, it has the potential to cause harm, and physicians should be aware of the degree of this risk when considering treatment options and to inform subsequent care.

Hypoglycemia was seen at a relatively high frequency in patients receiving intravenous insulin in the setting of hyperkalemia (17%) compared to patients that did not receive insulin (4%). The rate of hypoglycemia in our study is comparable or higher than what has been described in smaller studies that included non-emergency department patients, which reported rates of 17%, 8.7%, and 13% [8-10]. Another study that included emergency department patients described a higher rate of hypoglycemia, though this study was limited to patients with renal insufficiency [11].

As the manifestation of hypoglycemia may be delayed, and ED patients frequently experience handoffs and boarding, it could be hypothesized that hypoglycemia is more likely to result in clinical harm in the ED, and therefore identifying this phenomenon in the ED is of importance. Hypoglycemia may occur in this setting due to inadequate administration of glucose to replace the glucose consumed by the exogenous insulin, or the prolonged half-life of insulin in end-stage renal disease [14].

In this study, a lower glucose value prior to insulin, lower D50 dose and higher insulin dose were all independently associated with the development of hypoglycemia. The association between glucose value prior to insulin and hypoglycemia has been described in earlier investigations, however this finding had not previously been examined using a multivariate analysis, as was done in this study [8-10]. The dose of D50 was not associated with hypoglycemia in a previous analysis, and other studies have not described the relationship between these two variables [10]. Of note, the multivariate analysis in our study helped clarify the relationship between D50 dose and hypoglycemia, as the group that experienced hypoglycemia received, on average, a higher dose of D50, however when examined independently, lower doses of D50 were instead associated with increased odds of hypoglycemia. With regards to the dose of insulin administered, in a non-randomized retrospective study of a quality improvement intervention, a lower rate of hypoglycemia was seen in a cohort of patients who received 5 units of insulin compared to 10 units, while other studies have not independently analyzed this association [17]. Our findings provide support for institutional protocols that aim to decrease the rate of hypoglycemia by administering more dextrose and less insulin during shifting, however the efficacy of these regimens in respect to other clinical outcomes is not yet adequately described.

Furthermore, there was no association found between the development of hypoglycemia and age, a history of ESRD, or diabetes. The lack of association with ESRD is not previously described, and association with other variables is inconsistently noted or not explored in other studies. Our results support the notion that variables related to treatment (dose of insulin, dose of D50) and current patient condition (pre-treatment glucose) have a greater influence on the rate of hypoglycemia than

**Table 2**
For patients with hyperkalemia that received insulin, comparison of characteristics in cohort that became hypoglycemic with those that did not become hypoglycemic.

| | Hypoglycemia cohort (n = 68) | No hypoglycemia cohort (n = 341) | Difference in median or mean (95% CI) |
|---|---|---|---|
| Patient glucose prior to insulin, median (IQR), mg/dL | 99 (82–118) | 142 (104–318) | 45 (33–59) |
| Amount of insulin administered, mean ± SD (range), units | 10.3 ± 5.0 (5–50) | 9.6 ± 3.5 (5–57) | −0.7 (−1.7 to 0.3) |
| Amount of D50 administered, mean ± SD (range), g | 40 ± 25 (0−100) | 33 ± 28 (0–100) | −6.3 (−13.5 to 1) |

**Table 3**
Generalized estimating equation results for variables associated with the odds of development of hypoglycemia after insulin administration.

| | Adjusted odds ratio | 95% confidence interval |
|---|---|---|
| Glucose value prior to insulin (10 mg/dL) | 0.90 | 0.85 to 0.96 |
| Dose of insulin administered (units) | 1.07 | 1.01 to 1.14 |
| Dose of D50 administered (g) | 0.98 | 0.97 to 0.99 |
| Diabetes mellitus (yes/no) | 0.61 | 0.28 to 1.31 |
| ESRD (yes/no) | 1.32 | 0.65 to 2.67 |
| Age (years) | 0.99 | 0.97 to 1.02 |

ESRD: end-stage renal disease; IV: intravenous; D50: 50% dextrose.

patient-specific characteristics (age, history of ESRD, history of diabetes).

### 4.2. Limitations

This investigation has several limitations to note. Hypoglycemia is itself an adverse outcome that is associated with poor outcomes [18-20]. While the prevention of hypoglycemia is an important patient safety goal, this study did not specifically look at outcomes that are more patient-centered, such as hypoglycemic encephalopathy, mortality, or cost. Some patients who received intravenous insulin did not have a glucose value obtained within 3 h. For the purposes of our analysis, we classified those patients as not having experienced hypoglycemia. However, it is possible that some of these patients did develop subclinical hypoglycemia during this time period and therefore our results may represent an underestimation of the true frequency of hypoglycemia in this patient population. We assumed that the administration of intravenous insulin was given with the intent of treating hyperkalemia, however it is possible that a certain number of patients may have had intravenous insulin administered primarily for other purposes, such as the treatment of diabetic ketoacidosis. While this may introduce some heterogeneity in the study population, it does not alter the primary finding regarding the frequency of hypoglycemia in patients with hyperkalemia receiving intravenous insulin.

### 4.3. Future directions

The rate of hypoglycemia experienced by patients in this study highlights the risk associated with a common ED treatment. These findings should not necessarily discourage the use of insulin by emergency medicine providers in the treatment of clinically significant hyperkalemia, but rather should prompt physicians to adopt practices to mitigate this risk. An example of this would be emergency departments developing standard practices for checking glucose at frequent and regular intervals following the administration of intravenous insulin.

Recommendations vary regarding the optimal dosing of insulin and dextrose for the acute treatment of hyperkalemia. The American Heart Association has recommended 10 units of insulin to be mixed with 25 g of D50 and infused over 15 to 30 min, and the European Resuscitation Council offers a similar recommendation in their 2015 guidelines [21,22]. A recent systematic review found limited evidence to support a specific insulin and dextrose regimen [23]. A continuous insulin infusion has been advocated by some authors, however this is a labor-intensive intervention that may be impractical in emergency departments [24]. A recent retrospective study has suggested that 5 units of insulin may be equally effective in lowering potassium, with lower rates of hypoglycemia, however the non-randomized design limits the conclusions that can be drawn [11].

This methodology of our study does not allow for specific recommendations to be made regarding optimal doses of medications. Future research should compare treatment protocols involving different doses of insulin and/or D50 using a prospective, randomized or pseudo-randomized methodology. In addition to the rate of hypoglycemia, it would be important to analyze the efficacy of different doses of insulin and dextrose on lowering potassium and other clinically significant outcomes.

Finally, this study occurred at a single institution. While the patient characteristics are likely similar to other emergency departments, this finding should be replicated in other settings to greater support the external generalizability of the results.

## 5. Conclusion

In this emergency department cohort, hypoglycemia occurred frequently after insulin was administered for hyperkalemia. The pre-treatment glucose, dose of insulin, and the dose of D50 administered were independently associated with the development of hypoglycemia. This study adds an additional emergency department perspective to the relatively little evidence to date that describes this complication. While intravenous insulin continues to be a critical therapy for ED patients with hyperkalemia, physicians should be aware of the frequency of adverse events associated with its use, and adopt strategies to mitigate the risk involved. This work suggests that variables related to the treatment and have a greater influence on the development of hypoglycemia than patient-specific characteristics. This area of investigation is ripe for further quality improvement research to help define a standard of care that minimizes the risk of complication while maintaining efficacy of this treatment.

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