Efficacy of standard- vs reduced-dose insulin for treatment of hyperkalemia: A quasi-experiment

Sara Catherine Pearson, PharmD, BCPS, The University of Tennessee Medical Center, Knoxville, TN, USA

Kristin O'Connor, MD, The University of Tennessee Graduate School of Medicine, Knoxville, TN, USA

Kimberly Keller, PharmD, BCPS, The University of Tennessee Medical Center, Knoxville, TN, USA

T.J. Hodge, PharmD, The University of Tennessee Medical Center, Knoxville, TN, USA

Ross Nesbit, MD, The University of Tennessee Medical Center, Knoxville, TN, USA

Address correspondence to Dr. Pearson (sara.catherine.pearson@gmail.com).

ABSTRACT

Purpose. Hyperkalemia more commonly affects patients with a glomerular filtration rate of less than 60 mL/min. Using intravenous (IV) insulin to shift potassium intracellularly may cause hypoglycemia, requiring additional treatment or longer hospitalization. Literature on insulin dosing in this context is limited, with one previous study indicating that 5 units of IV insulin might be as effective and result in less hypoglycemia than the standard dose of 10 units of IV insulin. The hyperkalemia treatment pathway at our institution was revised in May 2018 to include a reduced-dose option (5 units of insulin) for patients with end-stage renal disease. This study aimed to compare the prevalence of hypoglycemia between patients who received standard-dose vs reduced-dose IV insulin.

Methods. This single-center, retrospective, quasi-experimental study evaluated the impact of revision of the hyperkalemia treatment pathway by assessing rates of hypoglycemia during the 6 months before and after implementation of the revised pathway. The primary endpoint was prevalence of hypoglycemia, defined as a blood glucose level of less than or equal to 70 mg/dL.

Results. There was no statistically significant difference in the occurrence of hypoglycemia when comparing the pre- and postimplementation groups (36 [17.7%] patients vs 34 [18.7%] patients; *P* = 0.7924). The postimplementation group had a statistically significant lower reduction in potassium levels after treatment than the preimplementation group (mean [interquartile range], –0.9 [–1.3, –0.5] mEq/L vs –0.6 [–1.2, –0.2] mEq/L; *P* = 0.0095). Baseline potassium levels were similar between the groups.

Conclusion. Administration of reduced-dose IV insulin for treatment of hyperkalemia was significantly less effective in lowering serum potassium levels and did not decrease prevalence of hypoglycemia. When accounting for potential confounders, the only variable that was associated with hypoglycemia was pretreatment glucose level.

Keywords: hyperkalemia, hypoglycemia, insulin**,** potassium binders, renal impairment

The incidence of acute hyperkalemia in hospitalized patients is well documented in the literature, occurring in 1% to 10% of patients.[1] Hyperkalemia disproportionately affects hospitalized patients with renal dysfunction, more commonly occurring in patients with a glomerular filtration rate (GFR) of less than 60 mL/min.[2-7] Treatment options for hyperkalemia consist of calcium gluconate, intravenous (IV) insulin, loop diuretics, albuterol, and potassium binders.[8,9] Although hemodialysis is the most effective method for removing potassium in a patient with end-stage renal disease (ESRD), this may not be a readily available option depending on hospital resources. Use of IV insulin can effectively shift potassium into the intracellular space, but this carries the risk of hypoglycemia.[9,10] Insulin's propensity to cause hypoglycemia, cited in the literature as occurring at a rate of 6% to 20%, may warrant additional treatment and potentially prolong the hospital stay.[11-13] Patients with renal impairment are thought to be more susceptible to hypoglycemia owing to a reduced capacity to break down insulin.[12] Theoretically, patients with renal dysfunction may require reduced doses of IV insulin for the management of hyperkalemia, but data in support of this are limited. Several small studies have demonstrated that 5 units may be equally as effective as 10 units in reducing hyperkalemia while minimizing incidence of hypoglycemia.[9-12] Garcia et al[9] evaluated the use of 5 units (n = 92) vs 10 units (n = 309) of IV insulin and found no significant difference in potassium reduction between the groups (–0.096 mEq/L; P = 0.2210). Pierce et al[10] compared rates of hypoglycemia and severe hypoglycemia between patients with low estimated GFR (eGFR) when using 5 units (n = 71) vs 10 units (n = 78) of IV insulin. Rates of hypoglycemia were not different between the groups (16.7% and 19.7% with 10 and 5 units respectively; P = 0.79).

Despite the existing literature, the optimal dose of insulin in management of acute hyperkalemia remains unclear.

Because of concern regarding high prevalence of hypoglycemia in treatment of hyperkalemia, a multidisciplinary team was convened in the spring of 2018 to review and revise the emergent hyperkalemia treatment pathway at our institution. This pathway is available for all providers to use through computerized physician order entry and includes laboratory tests, diagnostic tests such as electrocardiography (ECG), and pharmacological treatments for hyperkalemia. The multidisciplinary team decided that there were 2 major changes that could be made in an effort to reduce the incidence of hypoglycemia. The first change was to increase the upper glucose limit at which dextrose would be administered before administration of IV insulin. Previously, the upper limit to administer dextrose was 200 mg/dL. As part of the pathway revision, this limit was raised to 250 mg/dL, increasing the number of patients who would receive dextrose before IV administration of insulin. The second major change was creation of an ESRD subphase that defaulted insulin dosing to 5 units and a non-ESRD subphase that defaulted insulin dosing to 10 units. Previously, all patients received 10 units of IV insulin via this pathway. The revisions to the emergent hyperkalemia treatment pathway were implemented in May 2018. The aim of this study was to evaluate the impact of these changes on the prevalence of hypoglycemia and reduction in potassium levels for all patients for whom this pathway was ordered and further add to the literature surrounding efficacy of reduced-dose insulin in hyperkalemia treatment.

Methods

Patient population. This was a single-center, retrospective, quasi-experimental study evaluating the impact of a revised hyperkalemia treatment pathway on the rate of hypoglycemia, defined as a blood glucose level of less than or equal to 70 mg/dL, at an academic medical center in the southeastern United States. Less than or equal to 70 mg/dL was chosen as the breakpoint for hypoglycemia because this is the number used at our institution to define hypoglycemia and reflects the definition established by the American Diabetes Association. Revisions to the emergent hyperkalemia treatment pathway were implemented at our institution on May 28, 2019. Data were collected for patients who received IV insulin via this pathway in the 6 months before pathway revision and the 6 months after pathway revision for a total of 12 months of data from November 28, 2018, to November 28, 2019. This study was approved by the institutional review board at our institution.

Patients were excluded if they did not receive IV insulin as part of the emergent hyperkalemia treatment pathway, did not have follow-up glucose and potassium levels documented within 6 hours of pathway initiation, or had received IV insulin within the previous 48 hours. Patients were identified by a pathway compliance marker that pulled all available patients for whom the hyperkalemia pathway was ordered within the study period. This method identified a total of 710 patients to be screened for inclusion. Of these patients, 204 patients were included in the preimplementation group and 182 patients were included in the postimplementation group. The reasons for exclusion are shown in Figure 1. The primary endpoint was prevalence of hypoglycemia. The secondary endpoints were length of stay and potassium level 6 hours after insulin administration.

Study design and methods. We investigated the difference in outcomes following revisions to the emergent hyperkalemia treatment pathway at our institution. Before revision, the pathway included orders for calcium gluconate 1,000 mg, insulin 10 units IV, sodium bicarbonate IV 50 mEq, 50% dextrose 25 g, and oral sodium polystyrene sulfonate (SPS). The threshold for administering dextrose before insulin was 200 mg/dL. After revision, the pathway included the same drug therapy, except it excluded sodium bicarbonate and oral SPS. Sodium bicarbonate was excluded because of conflicting evidence in the literature. SPS was changed to administration per rectum only owing to the need for faster onset of action. The threshold for administering dextrose before insulin was increased to 250 mg/dL, meaning that patients with higher glucose levels would now receive dextrose when they previously would not have. Additionally, the revised pathway included 2 subphases: a non-ESRD treatment subphase and an ESRD treatment subphase. The non-ESRD subphase included a default IV insulin dose of 10 units while the ESRD treatment subphase included a default IV insulin dose of 5 units.

Data were collected from the electronic medical record (EMR) and included demographic information, history of diabetes and/or ESRD, serum creatinine levels, potassium levels, glucose levels, timing of administration of medications, drugs commonly administered via the hyperkalemia pathway (ie, dextrose, sodium bicarbonate, inhaled albuterol, and SPS), length of stay, ECG changes, medications with the propensity to contribute to hyperkalemia (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, and sulfamethoxazole/trimethoprim), medications with the ability to affect glucose levels (ie, dextrose-containing continuous fluids and/or IV piggybacks, oral or IV steroids, fluoroquinolone antibiotics, and oral antidiabetic

agents), and comorbid conditions to calculate the Charlson Comorbidity Index (CCI). These data are shown in Tables 1-4.

On the basis of the available literature, we expected an effect size of 10%, correlating to an event rate of 20% in the preimplementation group and 10% in the postimplementation group.[11,12] Using a 2-tailed hypothesis, an alpha value of 0.05, a beta value of 0.20, and an equal allocation rate to the treatment arms, 199 participants were predicted to be required in each group to meet power, for a total sample size of 398.

Statistical analysis. All analyses were conducted using SAS (version 9.4[TS1M5]; SAS Institute, Cary, NC). All continuous variables were evaluated for normality using a Shapiro-Wilk test, a Kolmogorov-Smirnov test, and visual inspection of histograms. None of the continuous variables were found to have a normal distribution; thus, all between-group comparisons were performed with the Mann-Whitney *U* test. Continuous variable results are presented as median and interquartile range. Between-group comparisons of categorical variables were evaluated using a χ^2 or Fisher's exact test, as appropriate. The null hypothesis of no difference was rejected if the between-group comparison *P* value was less than 0.05.

Results

We identified 710 patients for whom the emergent hyperkalemia treatment pathway was ordered during the study period. A total of 324 patients were excluded. The primary reason for exclusion was absence of repeat glucose and/or potassium values after insulin administration (*n* = 170, 52%) (Figure 1). A total of 386 patients met the inclusion criteria, with

204 patients in the preimplementation group and 182 patients in the postimplementation group for analysis. Patient demographics were well balanced between the groups (Table 1), and use of medications that may contribute to hyperkalemia was the only statistically significant difference (Table 3). Specifically, use of potassium binders was significantly different between the groups, and there was higher use of oral SPS in the preimplementation group than in the postimplementation group (89 [43.6%] patients vs 54 [29.7%] patients; *P* = 0.0046). In the postimplementation group, there was significantly higher utilization of rectal SPS (3 [1.5%] patients vs 12 [6.6%] patients; *P* = 0.0093) and patiromer (1 [0.5%] patient vs 10 [5.5%] patients; *P* = 0.0032). This higher utilization of rectal SPS and patiromer in the postimplementation group is likely related to pathway changes that removed oral SPS from the pathway and added patiromer. The significant between-group differences can be attributed to the pathway revisions, although it is important to note that these agents may still be ordered by providers outside of the pathway.

There was no statistically significant difference in the occurrence of hypoglycemia between the preimplementation and postimplementation groups (36 [17.7%] patients vs 34 [18.7%] patients; *P* = 0.7924) (Table 5). Additionally, when comparing patients who received at least 10 units of insulin to those who received less than 10 units of insulin, there was no difference in the occurrence of hypoglycemia (60 [19.2%] patients vs 10 [13.5%] patients; *P* = 0.2511). A total of 82 patients were included in a subgroup analysis of patients with ESRD. Of these, 52 were in the preimplementation group and 30 were in the postimplementation group. When comparing the pre- and postimplementation groups, there was no difference with respect to the occurrence of hypoglycemia (18 [34.62%] patients vs 9 [30%] patients; *P* =

0.6684). In addition, there was no between-group difference in the reduction in potassium levels in the ESRD subgroup analysis. The reduction in potassium levels was –0.9 mEq/L vs –0.6 mEq/L in the pre- and postimplementation groups, respectively (median [interquartile range], –0.6 [–1.5, –0.350] mEq/L vs –0.4 [–0.9, –0.1] mEq/L; $P = 0.2708$).

We constructed a multivariable logistic regression model to predict the occurrence of hypoglycemia, including the following variables in the model: patient group, insulin dose, pathway appropriateness, and glucose level before insulin administration. The model was statistically significant (global null hypothesis: beta = 0, Wald $\chi^2 = 23.29$; $P = 0.0001$), and there was no evidence of lack of fit (Hosmer-Lemeshow goodness-of-fit $\chi^2 = 34.9801$, degrees of freedom = 8; $P < 0.0001$). The only variable in the model that was associated with hypoglycemia was the pretreatment glucose level. When controlling for all other variables in the model, for every 1 mg/dL increase in baseline glucose, the odds of developing hypoglycemia were 0.987 (95% confidence interval, 0.982-0.992). In the preimplementation group, the median pretreatment glucose level in patients who experienced hypoglycemia ($n = 36$) was 122.9 mg/dL as compared to a median of 175.8 mg/dL in patients who did not experience hypoglycemia ($n = 168$). In the postimplementation group, the median pretreatment glucose level was 122.1 mg/dL for patients who experienced hypoglycemia ($n = 34$) vs 163.5 mg/dL for those who did not ($n = 149$). Despite differences between the pre- and postimplementation groups, there was a wide gap in pretreatment glucose levels when comparing patients who experienced hypoglycemia to those who did not.

The postimplementation group had a statistically lower reduction in potassium levels after treatment than the preimplementation group (median [interquartile range], –0.9 [–1.3, –0.5] vs –0.6 [–1.2, –0.2]; *P* = 0.0095), although the 2 groups had similar baseline potassium levels (6.2 [5.9, 6.5] mEq/L vs 6.2 [5.8, 6.6] mEq/L in the pre- vs postimplementation group; *P* = 0.7841). As compared to patients who did not have ESRD at baseline, patients with ESRD had a statistically lower reduction in potassium levels (–0.9 [–1.3, –0.5] vs –0.6 [–1.0, –0.2]; *P* = 0.0078), which may potentially be attributed to their receiving a lower insulin dose. As compared to patients who received less than 10 units of insulin, patients who received at least 10 units of insulin had a statistically greater reduction in potassium levels (–0.6 [–0.9, –0.2] vs –0.8 [–1.3, –0.4]; *P* = 0.0078). There was no statistically significant difference in length of stay between the groups (6 [3.5, 13] days vs 7.5 [4, 11] days for the pre- and postimplementation groups, respectively; *P* = 0.4438).

Discussion

In this study, we investigated the difference in outcomes following revisions to the emergent hyperkalemia treatment pathway at our institution. Despite changes to this pathway, we found no difference in the prevalence of hypoglycemia between patient groups. The multivariable regression analysis performed demonstrated that, for every 1 mg/dL decrease in the baseline glucose level, the odds of developing hypoglycemia were 0.987 when all other variables were controlled. This led us to hypothesize that patients with lower baseline glucose levels may benefit from receipt of a higher amount of dextrose, 50 g instead of the current

standard of 25 g, before IV insulin administration. In the future, we may implement a dextrose scale in which 50 g is administered for blood glucose levels below 150 mg/dL, 25 g is administered for blood glucose levels of 150 to 250 mg/dL, and 12.5 g is administered for blood glucose levels of 251 to 300 mg/dL.

Additionally, we found that use of 5 units of IV insulin was less effective than use of 10 units in regard to reduction of serum potassium levels. It is important to note that changes to the pathway resulted in significantly lower utilization of IV sodium bicarbonate and oral SPS. Although these agents lack robust evidence for efficacy in treatment of hyperkalemia, the between-group differences in use of these agents may have been a confounding factor in our results. We also note that the onset of action of SPS, when given rectally, is 1 to 2 hours, whereas that for patiromer is 6 to 7 hours.[16] In the acute treatment setting, we feel that the difference in reduction of potassium levels between groups could be a significant finding. Inadequate potassium reduction may require additional treatment and may increase the risk of adverse outcomes from additional treatment or prolonged time before resolution of hyperkalemia. Even when accounting for patients with ESRD, the potassium reduction was significantly less in patients who received less than 10 units of IV insulin.

This study was inherently limited by the inability to control for external factors. The retrospective nature of this study precluded the ability to control for variables such as timely laboratory draws or recording of medication administration. Serum potassium levels were collected at the time point nearest insulin administration if this was within 6 hours, but many patients were excluded because they did not have follow-up laboratory results recorded within

this time window. We feel that, although there are many factors that may contribute to this delay, there is significant room for improvement in this area. In a controlled clinical setting, all patients who received this treatment pathway would have follow-up laboratory testing. Multiple factors may have contributed to missing laboratory results, including patients transferring floors, patients leaving the floor for imaging or dialysis, or hemolysis of samples.

Additionally, providers can order select items and modify orders within the treatment pathway. Although our aim was to compare the outcomes of the original and revised pathways, providers' clinical decision-making would impact whether a patient received the treatment pathway as it was built or received a modified version of the pathway, which could impact results. For patients without documented ESRD in the EMR, we were unable to determine whether their renal impairment was acute or chronic in nature. Related to this, we also were unable to identify the chronicity of hyperkalemia or quantify how often or recently a patient might have received treatment for hyperkalemia. Our hypoglycemia results are reported as any patient with glucose levels less than or equal to 70 mg/dL; however, our institutional policy states that the first treatment that nurses should provide to patients is 4 ounces of orange juice, which is often not easily viewable in the EMR. Administering orange juice would provide an additional 3.3 mEq of potassium to a patient who is already hyperkalemic. Unfortunately, we were not able to collect this information on patients or control for this confounding factor. We tracked patients who required IV dextrose for hypoglycemia and were able to quantify how much dextrose they required for treatment; however, we were not able to quantify how often nonpharmacological treatment was utilized for patients with hypoglycemia.

Conclusion

Changes to the hyperkalemia treatment pathway at our institution did not result in a significant reduction in the incidence of hypoglycemia. Utilizing 5 units of IV insulin was less effective at reducing serum potassium levels than using 10 units of IV insulin. The findings of this study, and other studies evaluating lower insulin doses, will need to be validated in future studies to determine the most appropriate dosing of IV insulin and dextrose for safe and effective treatment of acute hyperkalemia.

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Disclosures

The authors have declared no potential conflicts of interest.

Additional information

This research was conducted ethically in accordance with the World Medical Association

Declaration of Helsinki and approved by the institutional review board at the University of Tennessee Medical Center.

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Figure 1. Study population. IV indicates intravenous.

Key Points

- Despite emerging literature, the optimal dose of insulin in management of acute hyperkalemia in patients with impaired renal function remains unclear.
- Changes in the hyperkalemia treatment pathway were implemented to reduce the incidence of hypoglycemia, including a reduced insulin dose (5 units) and a higher threshold for administering dextrose before insulin.
- Np significant change was found in the prevalence of hypoglycemia, although patients who experienced hypoglycemia tended to have a lower pretreatment blood glucose level than patients who did not.

Sara Catherine Pearson, PharmD, BCPS, is a clinical pharmacist specializing in cardiology and serves as the research coordinator for the postgraduate year 1 residency program at the University of Tennessee Medical Center in Knoxville, TN. She is also an assistant professor at the University of Tennessee Health Science Center College of Pharmacy on the Knoxville campus. Dr. Pearson received her bachelor of science degree in pharmaceutical sciences in 2015 and her doctor of pharmacy degree in 2018, as a cum laude graduate, from the University of Louisiana at Monroe College of Pharmacy. She then completed her postgraduate year 1 pharmacy residency in 2019 and her postgraduate year 2 internal medicine pharmacy residency in 2020 at the University of Tennessee Medical Center in Knoxville, TN. Her current research interests include acute and chronic management of hyperkalemia, transitions of care in heart failure, and resident and student learning styles.

Table 1. Baseline Characteristics

Characteristic[a]	**Preimplementation (*n* = 204)**	**Postimplementation (*n* = 182)**	***P* Value**
Age, median (IQR), years	65 (55, 72)	64 (52, 72)	0.7707
Female	79 (38.7)	74 (40.7)	0.6982
Race			0.4566
African American	27 (13.2)	17 (9.3)	NA
Hispanic/Latino	0	1 (0.6)	NA
White	174 (85.3)	161 (88.5)	NA
Unknown	3 (1.5)	3 (1.7)	NA
End-stage renal disease or received hemodialysis	52 (25.5)	51 (28.0)	0.5745
Diagnosis of diabetes	100 (49.0)	83 (45.6)	0.5024
Actual weight[b], median (IQR), kg	77 (63.5, 100.7)	84.8 (71.8, 101.4)	0.0588
Ideal body weight[b], median (IQR), kg	66.1 (54.7, 74.5)	66.1 (57, 75)	0.4440
Dosing weight[b], median (IQR), kg	71.5 (61.6, 83.5)	75.1 (66.5, 82.6)	0.2053
Serum creatinine at pathway initiation, median (IQR), mg/dL	3.0 (1.7, 6.7)	2.9 (1.6, 5.5)	0.5364
Creatinine clearance at pathway initiation[c], median (IQR), mL/min/1.73 m^2	19.5 (7.5, 36.5)	20 (8.8, 42.5)	0.3502
Charlson Comorbidity Index, median (IQR)	5 (4, 7)	5 (3, 7)	

Abbreviations: IQR, interquartile range; NA, not applicable.

[a]Data are shown as No. (%) unless indicated otherwise.

[b]Data for weight are shown for a subset of patients, including for 145 and 172 patients for actual weight, 132 and 69 patients for ideal body weight, and 132 and 69 patients for dosing weight in the pre- and postimplementation groups, respectively.

[c]Data for creatinine clearance are shown for a subset of patients, including for 148 and 86 patients in the pre- and postimplementation groups, respectively.

Table 2. Use of Oral or Intravenous Antihyperglycemic Agents, Corticosteroids, or Dextrose-Containing Fluids Within the 24 Hours Before Hyperkalemia Treatment

Treatment[a]	Preimplementation (*n* = 204)	Postimplementation (*n* = 182)	*P* Value
Antihyperglycemic			
IV insulin outside the pathway	8 (3.9)	7 (3.9)	0.9695
Subcutaneous insulin	57 (27.9)	51 (28.0)	0.9859
Oral hypoglycemic agent	11 (5.4)	16 (8.8)	0.1912
None of the above	138 (67.7)	118 (64.8)	0.5595
Corticosteroids in the previous 24 hours			
IV steroids	30 (14.7)	20 (11.0)	0.2777
Oral steroids	15 (7.4)	20 (11.0)	0.2143
None of the above	161 (78.9)	145 (79.7)	0.8562
Dextrose-containing fluids[b]	51 (25)	34 (18.7)	0.1348

Abbreviation: IV, intravenous.

[a]Data are shown as No. (%).

[b]Dextrose-containing fluids were defined as receipt of any intravenous fluids containing dextrose, ie, intravenous antibiotics diluted in dextrose or 5% dextrose in water as a continuous fluid.

Table 3. Agents Possibly Contributing to Hyperkalemia Administered Within 24 Hours Before Hyperkalemia Treatment

Agent[a]	Preimplementation (*n* = 204)	Postimplementation (*n* = 182)	*P* Value
Angiotensin-converting enzyme inhibitor	29 (14.2)	24 (13.2)	0.7694
Angiotensin receptor blocker	10 (4.9)	16 (8.8)	0.1280
Potassium-sparing diuretic	7 (3.4)	21 (11.5)	0.0022
Sulfamethoxazole/trimethoprim	6 (2.9)	5 (2.3)	0.9090
Nonsteroidal anti-inflammatory drug	2 (1.0)	19 (9.9)	<0.0001
Potassium supplement	12 (5.9)	23 (13.2)	0.0138
None	150 (73.5)	104 (57.1)	0.0007

[a]Data are shown as No. (%).

Table 4. Hyperkalemia Treatment Modalities Utilized

Hyperkalemia Treatment	Preimplementation (*n* = 204)	Postimplementation (*n* = 182)	*P* Value
Cation exchangers			
Oral sodium polystyrene sulfonate	89 (43.6)	54 (29.7)	0.0046
Patiromer	1 (0.5)	10 (5.5)	0.0032
Sodium zirconium cyclosilicate	0 (0)	0 (0)	NA
Rectal sodium polystyrene sulfonate	3 (1.5)	12 (6.6)	0.0093
None	111 (54.4)	107 (58.7)	0.3863
Other therapy			
Albuterol	5 (2.5)	6 (3.3)	0.6181
Intravenous sodium bicarbonate	89 (43.6)	33 (18.1)	<0.0001
Insulin (units)[b]	10 (10, 10)	10 (5, 10)	<0.0001
Dextrose before insulin (g)	25 (25, 25)	25 (25, 25)	0.0468

Abbreviation: NA, not applicable.

[a]Data are presented as No. (%) unless indicated otherwise.

[b]Data are presented as parametric data; mean in postimplementation group = 7.8 units.

Table 5. Change in Potassium and Glucose Levels After Pathway

Measure[a]	Preimplementation (*n* = 204)	Postimplementation (*n* = 182)	*P* Value
Potassium levels, mEq/L			
Potassium before pathway	6.2 (5.9, 6.5)	6.2 (5.8, 6.6)	0.7841
Potassium after pathway	5.3 (4.8, 5.8)	5.4 (4.9, 6.0)	0.1155
Change in potassium	–0.9 (–1.3, –0.5)	–0.6 (–1.2, –0.2)	0.0095
Blood glucose levels, mg/dL			
Glucose level before pathway	149 (113.5, 203.0)	135.5 (103, 190)	0.0731
Glucose level 30 min after insulin	161 (115, 208.5)	159.5 (100, 191)	0.08630
Glucose level after pathway (at 4-6 hours)	130.5 (95.5, 189)	132.5 (100, 191)	0.08734
Change in glucose (before to after pathway)	–13 (–45, 16)	–5 (–34, 23)	0.0692

[a]Data are shown as median (interquartile range).

Figure 1