Evaluation of the Impact of an Inpatient Hyperglycemia Protocol on Glycemic Control

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ABSTRACT - Purpose: Inpatient hyperglycemia is associated with poor outcomes. Existing research assessing inpatient hyperglycemia protocols has shown improvements in average blood glucose levels with inconsistent results regarding rates of hypoglycemia and hyperglycemia. The objective of this study was to evaluate the impact of an inpatient hyperglycemia protocol on glycemic control. **Methods:** This retrospective cohort study at a large, community teaching hospital included adult patients in non-critical care units requiring insulin administration for glycemic control. The intervention examined was utilization of an inpatient hyperglycemia protocol, comprised of a computerized physician order entry order set and provider education at the time of implementation. Two cohorts, a pre-protocol implementation group and a post-protocol implementation group, were compared. The primary outcome was the incidence of blood glucose values within 70-180 mg/dL over a 72-hour period between groups. Key secondary outcomes included the incidence of hypoglycemia (less than 70 mg/dL), severe hyperglycemia (above 300 mg/dL), total insulin use, and hospital length of stay. **Results:** The primary outcome was significantly improved following protocol implementation (54.2% vs. 58.4%, $p = 0.001$). Compared to the pre-protocol group, the post-protocol group had lower incidence of hypoglycemia (3.1% vs. 1.2%, $p < 0.001$), severe hyperglycemia (9.9% vs. 6.7%, $p < 0.001$), less total insulin use (1.1 units/kg vs. 0.6 units/kg, $p < 0.001$), and shorter length of stay (5.1 days vs. 3.7 days, $p < 0.001$). **Conclusions:** The implementation of an inpatient hyperglycemia protocol was associated with improved glycemic control, decreased incidence of both hypoglycemia and severe hyperglycemia, and less total insulin use.

INTRODUCTION

It is estimated that over 30.2 million Americans have diabetes (1). Hyperglycemia in hospitalized patients with and without diabetes is associated with poor outcomes, including increased risk of infection and mortality, and patients with diabetes are more likely to be hospitalized and experience longer lengths of stay (2-4). In fact, 22% of all inpatient stays are incurred by patients with diabetes, and these hospitalizations account for 43% of the $245 billion in diabetes-associated healthcare costs annually (3, 5).

The American Diabetes Association (ADA) Standards of Care recommend the use of scheduled basal, prandial, and correctional insulin to maintain random blood glucose levels of less than 180 mg/dL in non-critically ill hospitalized patients (3). The American Association of Clinical Endocrinologists (AACE) and the ADA published the Consensus Statement on Inpatient Hyperglycemia in 2009 to address appropriate management of inpatient hyperglycemia beyond insulin ordering. The statement endorses the use of electronic health records and computerized physician order entry (CPOE) programs containing protocols, algorithms, and decision support tools to enhance glycemic control (6).

Though nearly all previously published studies examining inpatient hyperglycemia protocols have reported decreased mean blood glucose levels and increased number of blood glucose values within goal range, there are discrepancies in other blood glucose-related outcomes (7-9). One of the largest studies to date evaluating the impact of a hyperglycemia protocol found decreased rates of severe hyperglycemia with no difference in hypoglycemia (7). Conversely, other studies have shown a decrease in hypoglycemic events but no change in severe hyperglycemia (8, 9).

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In addition to the variable rates of hypoglycemia and severe hyperglycemia, blood glucose goal ranges also differ throughout the current literature (7-13).

Glucometric data has been the primary focus of prior research with large sample sizes, but studies with smaller populations have additionally analyzed other non-blood glucose related outcomes. Among these patient-centered endpoints are the utilization of correction insulin-only regimens, basal and prandial insulin use, and in-hospital length of stay (10-13). Over the last two decades, inpatient hyperglycemia protocols have been established at numerous institutions with the goal of improving inpatient glycemic control. Mercy Hospital St. Louis implemented an inpatient hyperglycemia protocol in November 2013. The purpose of this research was to evaluate the impact of an inpatient hyperglycemia protocol on glycemic control at a large, community teaching institution through the examination of blood glucose values, insulin orders, and patient-centered outcomes.

METHODS

The inpatient adult hyperglycemia protocol at Mercy Hospital St. Louis includes an insulin order set within a CPOE. The order set consists of nursing communications and contingencies (i.e. monitoring and holding parameters, administration instructions, provider communication requirements), basal, prandial, and correction insulin orders, point-of-care blood glucose monitoring frequencies based on patients' nutritional statuses, and other pertinent laboratory tests (i.e. basic metabolic panel, hemoglobin A1c). Providers received education at the time of protocol implementation highlighting the importance of scheduling basal and bolus insulin while taking patient-specific factors into account (i.e. age, renal function, clinical status). These recommendations, in addition to the advisory to discontinue prior-to-admission oral anti-hyperglycemic medications, are included within the electronic order set. Since its implementation, insulin may be ordered outside of the order set, but is inconvenient as the order set contains all necessary orders and communications in a single functionality. The order set does not assist in calculating insulin doses nor automatically apportion doses between basal and bolus insulin. Guidance on adjusting insulin regimens and setting glycemic targets is also not provided.

The goal metabolic outcome for non-critically patients per the inpatient hyperglycemia protocol is blood glucose levels between 70-180 mg/dL. Ranges for hypoglycemia (< 70 mg/dL), hyperglycemia (181-300 mg/dL), and severe hyperglycemia (> 300 mg/dL) are also outlined in the protocol. The monitoring parameters for the protocol span 72 hours upon its initiation.

This retrospective cohort study evaluated two groups, a pre-protocol implementation group and a post-protocol implementation group. The pre-protocol group consisted of patients admitted January–July 2013 to represent inpatient glycemic control immediately prior to protocol implementation. The post-protocol group included patients admitted January–July 2017 to allow time for the protocol to be implemented and consistently utilized by providers. The protocol has remained virtually unchanged since its implementation.

Each cohort was identified by insulin orders. The pre-protocol group consisted of patients with an order for any formulary, non-regular insulin, including insulin glargine, detemir, aspart, lispro, insulin aspart protamine/insulin aspart, and insulin lispro protamine/insulin lispro. The post-protocol group included patients with insulin ordered within the adult hyperglycemia protocol. A random number generator was used to randomize patients within each group. It was pre-determined that a maximum of 500 patients would be included in the final analysis.

Adult patients (≥18 years old) in non-critical care units requiring insulin administration for glycemic control were included. At least one documented point-of-care blood glucose value was required for inclusion. Exclusion criteria consisted of patients with orders for regular insulin infusions, patients on insulin pumps, diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, pregnancy, and enteral or parenteral nutrition requirement.

All serum and point-of-care blood glucose values over a 72-hour period were recorded for patients meeting inclusion criteria. In the post-protocol implementation group, 72-hour blood glucose level collection began when patients were initiated on the inpatient hyperglycemia protocol, correlating with the first ongoing insulin order. Thus, 72-hour blood glucose level collection began when the first ongoing insulin order was placed in the pre-protocol implementation group to maintain consistent recording amongst cohorts. Numerous serum and point-of-care values recorded within a

one-hour time frame were not included except for in the treatment and monitoring of a hypoglycemic event. Orders for oral anti-hyperglycemic agents did not impede inclusion if the medication was administered after the initial 72-hour period.

The primary outcome was to compare the difference in the incidence of blood glucose values between 70-180 mg/dL over a 72-hour period between groups. Blood glucose-related secondary outcomes consisted of the incidence of hypoglycemia, hyperglycemia, and severe hyperglycemia. Other secondary outcomes included the difference in patients receiving basal and prandial insulin regimens, correction-insulin units administered, transfer to a higher level of care for the purpose of receiving an insulin infusion for glycemic control, 30-day readmission for a hyperglycemia-related event, in-hospital length of stay, and in-hospital mortality.

Descriptive statistics using proportions and means with standard deviations were utilized to assess baseline characteristics as appropriate. Chi-square and Fisher's exact tests were used for categorical data, and Student's t-tests were used for continuous data while comparing patient data and clinical outcomes between groups. A p-value < 0.05 was considered significant with 95% confidence intervals. All data analysis was performed with SPSS® software. This research was approved by the Institutional Review Boards at Mercy Hospital St. Louis and the St. Louis College of Pharmacy.

RESULTS

Five-hundred patients were included in the final analysis (pre-protocol n = 250, post-protocol n = 250). Five-hundred ninety-six charts were reviewed in the pre-protocol group and 465 charts in the post-protocol group. Patients were primarily excluded for admission to a critical care unit, administration of an oral anti-hyperglycemic agent, or no insulin administered within the 72-hour collection period (Figure 1). Baseline characteristics were similar between groups with the exception of age and no previous diagnosis of diabetes mellitus upon admission (Table 1). The most common diagnosis-related groups for the entire cohort included chest pain (n = 33, 6.6%), congestive heart failure (n = 22, 4.4%), cellulitis (n = 21, 4.2%), cerebrovascular accident (n = 18, 3.6%), and abdominal pain (n = 17, 3.4%).

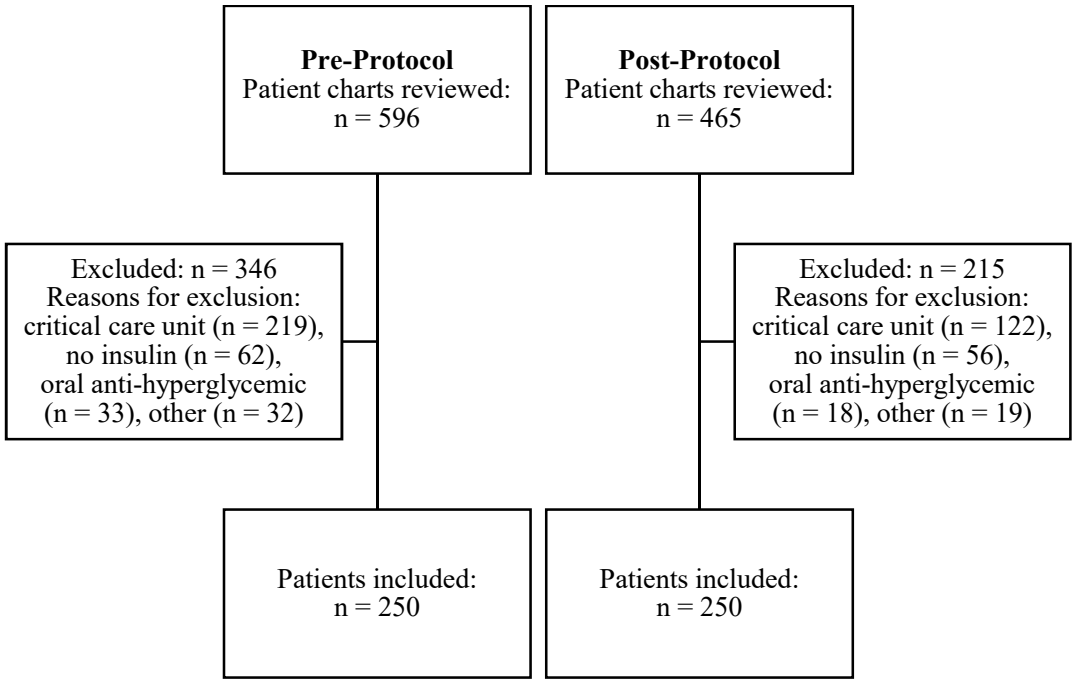

Figure 1. Study Populations by Protocol Implementation Cohort. Including 500 patients (pre-protocol n = 250, post-protocol n = 250) in the final analysis was pre-determined. Five-hundred ninety-six patients' charts were reviewed in the pre-protocol group, and 465 were reviewed in the post-protocol group. The primary reasons for exclusion included admission to a critical care unit, administration of an oral anti-hyperglycemic agent, or no insulin administered during the 72-hour blood glucose collection period.

Table 1. Baseline Characteristics

	Pre-Protocol (n=250)	Post-Protocol (n=250)	p-value
Age - years ± SD	62.5 ± 14.0	65.4 ± 15.1	0.027
Male sex - n (%)	123 (49.2)	131 (52.4)	0.720
Weight - kg ± SD	96.0 ± 26.7	95.8 ± 38.5	0.942
BMI - kg/m^2 ± SD	31.9 ± 8.9	32.2 ± 8.6	0.724
Race - n (%)			0.137
Caucasian	199 (79.6)	178 (71.2)	
Black or African American	39 (15.6)	62 (24.8)	
PTA anti-hyperglycemic[a] - n (%)			
Insulin	132 (52.8)	136 (54.4)	0.807
Oral	109 (43.6)	134 (53.6)	0.074
Non-insulin injectable	5 (2.0)	11 (4.4)	0.134
PTA corticosteroid - n (%)	16 (6.4)	14 (5.6)	0.706
No diagnosis of DM - n (%)	18 (7.2)	3 (1.2)	0.001
Type 1 DM - n (%)	5 (2.0)	9 (3.6)	0.19
Type 2 DM - n (%)	227 (90.8)	238 (95.2)	0.097
Hemoglobin A1c - % ± SD	8.7 ± 8.2	8.9 ± 12.4	0.805
Renal function - n (%)			
eGFR < 30 mL/min/1.73 m^2	35 (14.0)	42 (16.8)	0.386
End-stage renal disease[b] - n (%)	15 (6.0)	17 (6.8)	0.715
NPO[c] - n (%)	117 (46.8)	106 (42.4)	0.322
Inpatient corticosteroid - n (%)	45 (18.0)	39 (15.6)	0.473
Pharmacologic agent for hypoglycemia - n (%)			
Glucagon	1 (0.4)	1 (0.4)	1.00
Dextrose	6 (2.4)	4 (1.6)	0.523

PTA: prior-to-admission; DM: diabetes mellitus; NPO: nothing by mouth
[a]Any order for the given anti-hyperglycemic agent prior-to-admission. Includes patients with multiple anti hyperglycemic prescriptions.
[b]eGFR < 15 mL/min/1.73 m^2 or need for dialysis
[c]Any NPO order within the 72-hour collection period. Patients may have also had oral diet orders during the 72-hour period.

The primary outcome was significantly improved following protocol implementation (54.2% vs. 58.4%, p = 0.001). Both the incidence of hypoglycemia (3.1% vs. 1.2%, p < 0.001) and severe hyperglycemia (9.9% vs. 6.7%, p < 0.001) were lower in the post-protocol group compared to the pre-protocol group (Figure 2). The incidence of use of a pharmacologic agent for hypoglycemia and the number of patients receiving inpatient glucocorticoids were similar between groups (Table 1).

Less total insulin was administered following protocol implementation (1.1 units/kg vs. 0.6 units/kg, p < 0.001). The number of patients receiving basal insulin was significantly higher in the pre-protocol implementation group (63.2% vs. 52.0%, p = 0.011), but more patients received scheduled prandial insulin in the post-protocol implementation group (2.8% vs. 27.6%, p < 0.001) (Table 2).

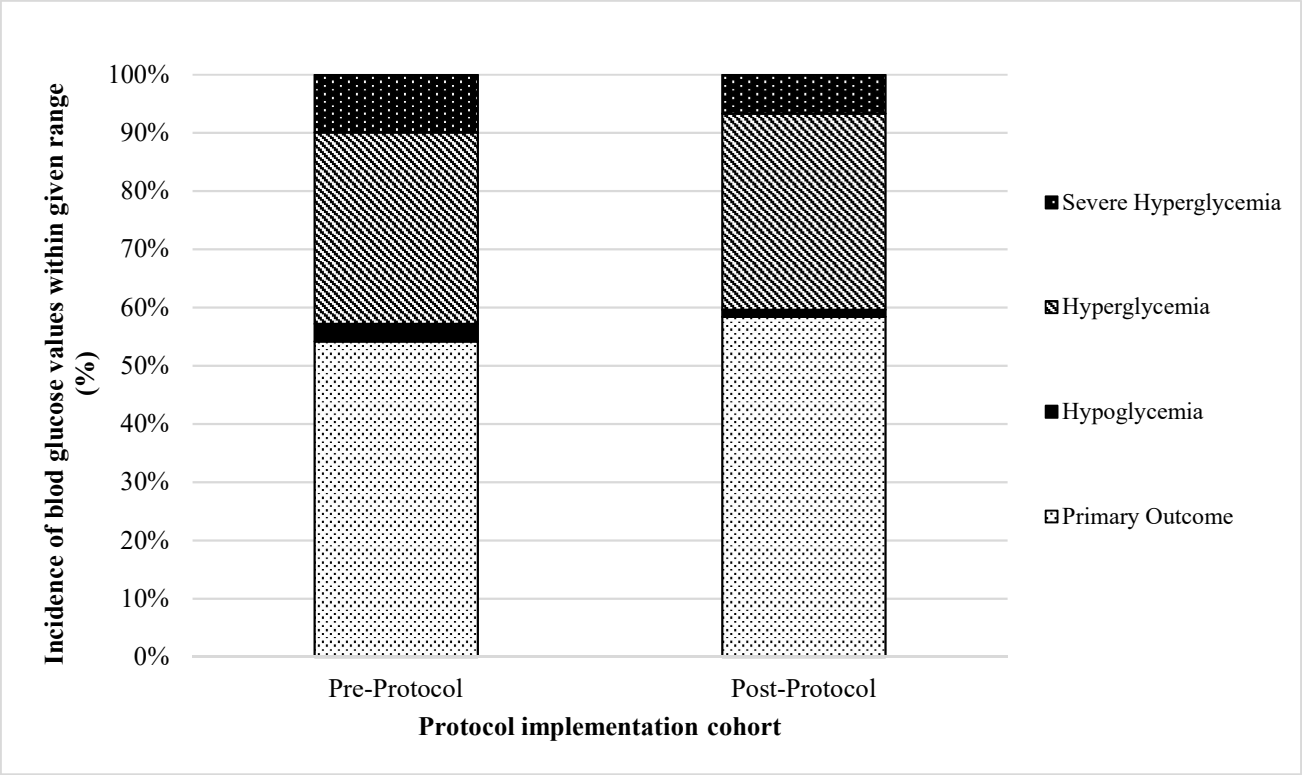

Figure 2. Percentages of Blood Glucose Values within a Given Range. The primary outcome (blood glucose between 70-180 mg/dL) significantly increased from pre-protocol to post-protocol implementation (54.2% vs. 58.4%, p = 0.001). Rates of hypoglycemia (3.1% vs. 1.2%, p < 0.001) and severe hyperglycemia (9.9% vs. 6.7%, p < 0.001) decreased following protocol implementation. The incidence of hyperglycemia (181-300 mg/dL) did not significantly differ between groups (32.8% vs. 33.7%, p = 0.454).

Table 2. Insulin Utilization

Insulin Orders	Pre-Protocol (n=250)	Post-Protocol (n=250)	p-value
Total			
Patients - n (%)	250 (100)	250 (100)	
Total units - units	25678	14247	< 0.001
Weight-based total - units/kg ± SD	1.1 ± 1.0	0.6 ± 0.8	< 0.001
Basal			
Patients - n (%)	158 (63.2)	130 (52)	0.011
Total units - units	13732	7546	0.297
Weight-based total - units/kg ± SD	0.6 ± 0.5	0.3 ± 0.3	< 0.001
Prandial			
Patients - n (%)	7 (2.8)	69 (27.6)	< 0.001
Total units - units	502	2278	< 0.001
Weight-based total - units/kg ± SD	0.02 ± 0.02	0.09 ± 0.06	< 0.001
Correction			
Patients (all) - n (%)	236 (94.4)	235 (94.0)	0.119
Patients (correction-only) - n (%)	89 (35.6)	106 (42.4)	0.119
Total units - units	11444	4410	< 0.001
Weight-based total - units/kg ± SD	0.4 ± 0.2	0.2 ± 0.1	< 0.001

The post-protocol implementation group had shorter average in-hospital lengths of stay (5.1 ± 4.8 days vs. 3.7 ± 3.6 days, $p < 0.001$). The incidences of transfer to a higher level of care for an insulin infusion (0.4% vs. 0%, $p = 0.317$), 30-day readmission (1.2% vs. 1.2%, $p = 1.00$), and in-hospital mortality (0.8% vs. 0%, $p = 0.499$) were minimal and did not differ between groups.

DISCUSSION

This study's evaluation of an inpatient hyperglycemia protocol demonstrated a post-protocol implementation association with improved glycemic control and decreased lengths of stay while using less total insulin in a moderately-sized study population. Studies with larger sample sizes have generally focused on glucometric data and have not been able to clinically correlate their findings with patient outcomes (7, 8). Conversely, smaller sample sizes have analyzed of insulin ordering patterns and patient-centered outcomes (10). This study's protocol is very similar to those previously described in smaller study populations but includes a larger sample size to attempt to associate glycemic control with clinical outcomes in a larger cohort (8, 10). Most patients included in this study did have a known diagnosis of diabetes prior-to-admission (92.8% pre-protocol and 98.8% post-protocol), so the significantly decreased length of stay following protocol implementation suggests that our institution's hyperglycemia protocol implementation may be associated with shorter hospitalizations in patients with diabetes mellitus.

This study also differs from prior research by demonstrating decreased rates of both hypoglycemia and severe hyperglycemia following the implementation of a hyperglycemia protocol (7-9). Previously, a large study Maynard et al., 2017 found decreased rates of severe hyperglycemia amongst seven of nine research hospitals while hypoglycemia remained unchanged at 3.6%. The low baseline rate of hypoglycemia in that study population may have attributed to no difference being noted, but our study's baseline hypoglycemia incidence was also low at 3.1% and a difference was found post-protocol implementation (7). It can be argued that the clinical inertia of the fear of inducing hypoglycemia may result from the implementation of a hyperglycemia protocol, but the decreased rate of hypoglycemia in our research was also accompanied by a significantly decreased incidence of severe hyperglycemia. However, the majority of the population in this study were diagnosed with diabetes prior-to-admission, had a mean body mass index (BMI) indicative of obesity, and had elevated hemoglobin A1c's, which may suggest an overall increased risk of insulin resistance, decreasing the likelihood of hypoglycemia.

The Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT-2 Trial), was a landmark prospective, randomized controlled trial that compared the efficacy and safety of a basal-bolus insulin regimen against the use of sliding scale insulin in non-critically ill patients with type 2 diabetes. Investigators found a significant increase in the number of blood glucose values less than 140 mg/dL with scheduled basal-bolus insulin regimens and no difference in the incidence in hypoglycemia (14). Apportioning insulin between basal and bolus insulins better mimics physiological insulin concentrations, thus more balanced insulin regimens may help obtain better glycemic control without increasing the amount of insulin administered (15). This concept affirms the results of our study as glycemic control was improved with an increase in scheduled prandial insulin ordered despite less total units of insulin given in the post-protocol group.

The significant increase in scheduled prandial insulin may be attributable to the inpatient hyperglycemia protocol's order set. The basal and prandial insulin orders precede the correction insulin ordering functions and require providers to offer reasoning if the two prior insulins are not selected. Decreases in the amount of correction-only insulin regimens following hyperglycemia protocol implementation has been previously shown, but the number of patients receiving correction-only regimens in our study did not differ from pre- to post-protocol implementation (35.6% vs. 42.4%, $p = 0.119$) (8, 10). However, the amount of correction insulin administered significantly decreased from pre- to post-protocol implementation (0.4 units/kg vs. 0.2 units/kg, $p < 0.001$), suggesting that the additional steps may have influenced the types of insulin ordered. Differing in-hospital lengths of stay and variability in patients' prior-to-admission anti-hyperglycemic regimens may also partially account for these observations.

The number of patients with orders for scheduled prandial insulin, though increased post-protocol implementation, is still relatively low in this research (2.8% vs. 27.6%, $p < 0.001$). Schnipper et al. also

saw an increase in scheduled prandial insulin following hyperglycemia protocol implementation but with a considerably higher baseline of patients with prandial insulin orders (45% vs. 70%) (10). This highlights an area of ongoing improvement within our institution but does suggest our current practice is more in alignment with the ADA Standards of Care post-protocol implementation (3).

The 72-hour blood glucose collection period utilized in this study differs from most of what is described in the literature. This method, in addition to the short lengths of stay many patients incurred, did not allow for calculation of a patient-day or day-weighted blood glucose means. However, the significant difference from pre- to post-protocol implementation in regard to the primary outcome does indicate that glycemic control is enhanced by protocol implementation in a short time span upon hospital admission. As true patient-day interpretations take patients' entire lengths of stay into account, the approach used in this study may have avoided confounders associated with prolonged hospital stays.

The inpatient hyperglycemia protocol, order set, and provider education were all implemented concomitantly. Therefore, it is difficult to determine which intervention was most highly associated with improved patient outcomes. A randomized, controlled trial evaluating medical residents' insulin ordering patterns with and without a CPOE program found a significant decrease in mean blood glucose levels in the intervention group. Both the control and intervention groups received education on basal-bolus insulin ordering implying that the CPOE helped improve glycemic control (11). However, this ordering system also included guidance on weight-based insulin dosing and appropriation between basal and prandial insulin which our order set does not include.

Insulin therapy is the mainstay of hyperglycemia treatment in hospitalized patients due to its route of administration and titratable ability (3). Insulin therapy does carry risks, most notably hypoglycemia, due to inappropriate dosing, monitoring, and adjustments based on patient-specific factors (15-17). Thus the importance of appropriately dosing insulin and monitoring blood glucose levels in the inpatient setting is crucial. Future research should evaluate inpatient insulin regimens per kilogram body weight, taking patient-specific factors and prior-to-admission anti-hyperglycemic regimens into account. Further assessment of adjustments in inpatient insulin regimens and investigation of pharmacists' involvement in insulin initiation and titration would also provide insight as to how hyperglycemia protocols are being utilized from an interdisciplinary perspective.

A strength of this research includes our institution's protocol's goals aligning with the AACE and ADA Consensus Statement, the ADA Standards of Care, and Society of Hospital Medicine Glycemic Control Task Force recommendations (3, 6, 15). Also, this was a randomized, moderately-sized chart review containing blood glucose data that was able to be compared to patient-centered outcomes. The 72-hour blood glucose collection period was of sufficient length to decrease the chance of Type I error, as well. In addition, both previous diagnoses of diabetes mellitus and general inpatient hyperglycemia were included, providing a representative sample of inpatients who receive insulin therapy.

Several limitations of this research have been identified. Although conducted at a large, community teaching hospital, the single-center nature of this study decreases its external validity. Also, as a retrospective chart review, point-of-care blood glucose monitoring frequency and documentation were unable to be controlled. More rigorous inpatient hyperglycemia research containing active surveillance of blood glucose values and frequent endocrinologist involvement has been documented in the literature but is less representative of clinical practice (14, 18). In addition, variable in-hospital lengths of stay in both protocol implementation groups were not conducive to analyzing the change in glycemic control from day one to day three of hospitalization.

CONCLUSION

The implementation of an inpatient hyperglycemia protocol was associated with improved glycemic control while decreasing total insulin use and in-hospital lengths of stay. As many studies have found better glycemic control following protocol implementation, our research carries implications that the creation of hyperglycemia protocols and electronic order sets is associated with shifts in insulin ordering patterns and improved patient outcomes.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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