Research & Reviews: Journal of Hospital and Clinical Pharmacy

Safety and Clinical Outcomes of Using an Automated Order Set for IV-SC Insulin Conversion in Hospitalized Patients: A Retrospective Cohort Study

Jayashri Sankaranarayanan, MPharm PhD[1,2]*, Kyle Lundgren PharmD[1#], Carrie Margeson, PharmD[1#], Mary Poonnose, PharmD[1#], Alicia Williams, PharmD[1#], Nicholas Tessier, PharmD, BCPS, MBA[2]

[1]Department of Pharmacy Practice, School of Pharmacy, University of Connecticut, Storrs, CT, USA
[2]Department of Pharmacy Services, Hartford Hospital, Hartford, CT, USA

Research Article

Received date: 01/05/2016
Accepted date: 10/05/2016
Published date: 16/05/2016

***For Correspondence**

Jayashri Sankaranarayanan, MPharm PhD, Associate Professor, School of Pharmacy, University of Connecticut, Storrs, CT, USA, Tel: 402-321-3777.

E-mail: jsankara@live.com

Keywords: IV-SC insulin conversion, Automated order set, Hypoglycemia, Hyperglycemia, Blood-glucose levels, Retrospective.

#Authors Equally Contributed and PharmD Candidates during the conduct of the study.

ABSTRACT

Objective: Two patient-groups (using, not using an automated order set) were compared for outcomes (differences in hypoglycemic events, hyperglycemic events, glucose-levels after IV- SC insulin conversion).

Methods: A retrospective cohort-study of automated order set versus non-order set critical-care patients receiving IV-insulin for at least 24-hours from January-May, 2014. Data included patients' age, race, comorbidities, IV-SC insulin conversion criteria (nutritional-status, prednisone-use, hypoglycemia-risk, and estimated-glomerular-filtration-rate), IV/SC insulin-doses, and outcomes (glucose-levels, number of hyperglycemic and hypoglycemic events,). A hypoglycemic and hyperglycemic event were each defined as a glucose level "<70 mg/dL counted every 2 hours" and ">180 mg/d counted every 3 or 8 hours", respectively.

Results: The differences between 24-hours post- minus pre- IV-SC conversion in 37 order set versus 59 non-order set patients were: 1) hypoglycemic events (percentage of patients with more events; 8%vs.5%, p>0.05) 2) hyperglycemic events at 8-hour window (percentage of patients with more events, 11%vs.32%,p=0.0171) and 3) average blood-glucose levels (median- difference 2.13 vs.15.46 mg/dL, p>0.05)

Conclusions: Despite the small sample size, the study demonstrated smaller (non-significant) fluctuations in blood glucose levels and significantly fewer hyperglycemic events in eligible automated order set vs. non-order set IV-SC converted patients. Providers using automated order sets for IV-SC conversion may get better clinical and safety outcomes.

INTRODUCTION

Glycemic control in hospitalized patients

Continuous intravenous (IV) insulin infusions effectively help achieve consistent and appropriate glucose levels that result in shorter hospital stays by avoiding the negative consequences of either hyperglycemia or hypoglycemia [1,2]. One study reported hyperglycemic events in 38% of all 2030 adult admitted patients (26% and 12% with a history and no history of diabetes) [3]. Patients with newly diagnosed hyperglycemia had a significantly greater mortality than those with established diabetes and those with normal glucose levels (16% versus 3% and 1.7% respectively) [3]. Further, hyperglycemia has been proven to lead to higher risk of other comorbidities such as wound infections in patients undergoing cardiac surgery, sepsis, renal failure, and

illness-related neuropathies in ICU patients [2]. However, the 2009 NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation) study found that the lower (81-108 mg/dL) versus more conventional blood glucose target (144-180 mg/dL) was associated with increased mortality (27.5% vs. 24.9%), and severe hypoglycemia (6.8% vs. 0.5%) [4], respectively. Therefore, insulin therapy targeted at higher blood glucose level (140-200 mg/dL) was a reasonable goal for ICU patients who have a lower risk of hypoglycemia than intensive insulin therapy [1]. After a period on IV insulin, it becomes necessary to transition patients over to basal and bolus subcutaneous (SC) insulin so patients can be moved to the general medicine floors and planned for discharge from the hospital.

Current literature

The most effective IV-SC transition protocol is not yet established as it is hospital specific. A review of the literature in the last ten years showed at least three studies including acute coronary syndrome and cardiac surgery patients from years 2009 to 2014. These studies validated the benefits of implementing IV-SC insulin conversion protocol in improving or maintaining glycemic control (in ~70%), with reduced hypoglycemic episodes (1-8%), and risk of sternal wound infections (0.8%) [5-7].

Rationale for hospitals to use automated order set

Because 16% of study patients had errors in applying the IV-SC insulin conversion protocol, Avanzini et al. suggested an innovative computer program to make protocol applications simpler and more precise [8]. Thus, one strategy to potentially limit both hyperglycemia and hypoglycemia in practice would be employ standardized, and automated IV-SC insulin conversion order sets to help physicians better prescribe and dose SC insulin, thereby reducing insulin dosing errors [9]. Automated order sets are expected to ensure effectiveness, safety and consistency in Insulin (a high-risk high-alert medication by the Joint Commission) use because of its risk of hypoglycemia [8].

Guidelines for insulin use and glycemic control in hospitalized patients

Most of the evidence on how to achieve optimal target blood-glucose levels in hospitals focuses on the use of insulin protocols. However, several published guidelines from various organizations recommend different blood glucose targets for critically ill patients [1,10-13]. The 2009 American Association of Clinical Endocrinologists and American Diabetes Association's (AACE/ADA), the 2011 guidelines of American College of Physicians, 2012 ADA, and the Society of Critical Care Medicine (SCCM) recommended a blood-glucose target of 140-180 mg/dL (vs. below 110 mg/dL) [8],140-200 mg/dL (vs. intensive glucose control at 80-110 mg/dL) [1], 140-180 mg/dL (with a more stringent goal of 110-140 mg/dL for some critically ill patients) [12], and 100-150 mg/dL (with absolute maximum of 180 mg/dL), respectively [13]. Continuous insulin infusion is the only method of insulin therapy developed specifically for the hospital population and is indicated for general preoperative, intraoperative, and postoperative care in patients with myocardial infarction or cardiogenic shock, and for those with critical care illnesses [14,15]. IV insulin is preferred in certain populations because of its rapid onset of action and ability to achieve glycemic control, preventing the detrimental outcomes (increasing morbidity, mortality) of poorly controlled hyperglycemia in the ICU [1]. However, IV insulin requires intense monitoring that can only be accommodated in ICU. While maintaining glucose control is critical, it is also imperative to avoid overly aggressive glycemic control as that can result in hypoglycemia episodes that increase the risk for dementia, transient ischemia, and catecholamine surges [1]. The most successful insulin infusion protocols share some important features that contribute to their acceptability and success using dynamic criteria that respond to individual patient's insulin responses and change in insulin needs over the course of treatment to ensure a stable plasma glucose level [16-18]. For instance, the Yale-New Haven Hospital protocol balances the rate of glucose change against the current blood glucose level and insulin infusion rate to determine highly individualized dose adjustments when needed [17]. The protocols designed by multidisciplinary groups, can be administered by nurses or other support personnel, use monitoring methods approved for use in most hospitals, and can be applied to all institutional departments from emergency departments to operating rooms and medical and surgical ICUs [17-25].

Study hospital protocol for automated order set

In March 2013, the study hospital implemented critical care insulin protocol step-by-step instructions on how to initiate, maintain and monitor IV insulin in critical care patients **(Appendix A)** which was adapted in part from the Yale-New Haven Hospital ICU Insulin Infusion Protocol for Adults. Recently, the study hospital implemented an automated electronic order set protocol to help physicians effectively individualize the transitioning of patients from IV-SC insulin maintaining standardization within the hospital. If providers choose to use the order set when converting from IV-SC insulin they are prompted to complete a short automated checkbox list of four criteria, including: patient nutritional intake status (PO or TPN), prednisone dose (checked if >10 mg/day), risk of hypoglycemia (checked if high risk), and eGFR. Based on this information, in addition to the patient's body mass index (BMI) and previous IV drip rate, the automated order set calculates basal and bolus insulin doses, ensuring an accurate IV-SC conversion.

Study rationale and objectives

The current literature demonstrates the beneficial impact of IV-SC insulin protocols like fewer hyperglycemic and hypoglycemic episodes. However, the majority of the studies [5-7] implemented the conversion via written protocols, rather than via an automated conversion order set. Additionally, much of the IV-SC insulin literature focuses on the protocol being utilized for particular patient

populations, such as post-cardiothoracic surgery patients where hyperglycemia, even independent of a past medical history of diabetes mellitus, is common [5-7]. However, there is limited literature on IV to SC insulin transition in other hyperglycemic patients with or without underlying diabetes, trauma, or sepsis who also require insulin therapy [10]. The current protocol and order set at the study hospital has been in place for over one year but has not yet been evaluated for effectiveness. The aim of the protocol is to keep blood glucose levels at 120-160 mg/dL. Further, over the past year, the order set has only been used by physicians 30-40% of the time when transitioning patients from IV-SC insulin.

There is a lack of literature and information in practice on whether using versus not using automated IV-SC insulin conversion order set protocol after its implementation was associated with better outcomes of insulin transition protocols beyond post-cardiothoracic surgery patients. Therefore, the study authors proposed a retrospective cohort study of all hyperglycemic patients on insulin and of those only the people who transitioned from IV to SC insulin at the hospital. The primary study objective is to compare the safety outcomes (differences in the number of hyperglycemic and hypoglycemic events 24 hours before and after the IV-SC conversion) in the group that used versus the group that did not use the automated conversion order set. The secondary objective was to compare the two groups for differences in the clinical outcome of average glucose level between 24 hours before and after the IV-SC conversion to determine if either group had better overall glucose control. The order set uses patient-specific criteria including hyperglycemia and hypoglycemia risk factors to help efficiently convert the insulin dosing. Therefore, we hypothesize that the using versus not using the automated order set will result in better clinical (glycemic control) and safety (lower hyper- and hypoglycemic events).

METHODS

Study design

A retrospective study design was used to examine the safety and clinical outcomes of the IV-SC insulin conversion order set in diabetic and non-diabetic critical care patients.

Study setting

The 867-bed study hospital is a teaching and leading tertiary medical center affiliated with a state university medical school, serving the New England region in the Northeast United States. The hospital has about 42,000 inpatient visits, 100,000 outpatient visits and 100,000 emergency department visits per year.

Data sources

The institutional review board at the study hospital approved the use of the de-identified data (obtained from the hospital Sunrise clinical manager (SCM) database including medication administration record (MAR) and pharmacy order database sources) as “exempt” from human subject research requirements.

Inclusion criteria

Patients >18 years of age were only eligible for the study if they had been on IV insulin for at least 24 hours and converted to appropriate SC insulins (Glargine or Detemir). Patients may have also been receiving sliding scale rapid acting insulins including Aspart and Lispro. However, this data were not collected.

Exclusion criteria

Patients <18 years old and >88 years old, having diabetic ketoacidosis or Diabetic Ketoacidosis or Hyperosmolar Hyperglycemic Syndrome, not on an insulin drip for 24 hours or more and not transitioned to SC insulin Glargine or Detemir were excluded.

Data collection procedures

Data was collected from January 1, 2014, to May 31, 2014, using non-interventional reviews of medication administration records and electronic pharmacy order database information.

Study variables

Data on patient demographics, criteria variables for IV-SC conversion for automated order set vs. non-order set patients and clinical and safety outcomes were extracted. Demographics included age (years), gender (female/male), race (Caucasian/other), reason for admission (cardiac-related or not), number of comorbidities, hospital length of stay (days), history of diabetes before hospital admission (yes/no), IV insulin drip rate (units/hour), IV insulin duration (hours), subcutaneous insulin dose over 24 hours (units), and SC insulin start time (hours). The variables associated with IV-SC insulin conversion were nutritional status (PO or Tube feed), steroid use (prednisone >10 mg; yes or no), high risk of hypoglycemia <70 mg/dL (yes or no), and estimated glomerular filtration rate (eGFR, mL/min). Corticosteroid conversion table [14] was used to compute the equivalent dose of prednisone corresponding to the steroid doses from the patients’ medication list in SCM database. For both order set and non-order set patients, number of hypoglycemic events (<70 mg/dL) 24 hours before and after IV-SC switch, and the number

of hyperglycemic events (>180 mg/dL) 24 hours before and after IV-SC switch were collected. A hypoglycemic event was "a glucose level <70 mg/dL with the next event being counted no sooner than 2 hours after the last event". Because of varying interpretations of hyperglycemic episode lengths by providers and literature [5], the hyperglycemic episodes were defined within an 8 hour time frame and a 3 hour time frame. Thus, a recorded hyperglycemic event was "a glucose level >180 mg/d with the next event being counted no sooner than 3 or 8 hours after the last event". The average of multiple points of care glucose levels (mg/dL) available for 24 hours before and 24 hours after the IV to subcutaneous conversion were collected. The study's safety outcome variables (defined as differences in number of hypo-, and hyperglycemic events and blood-glucose levels between 24 hours post- and pre- IV-SC insulin conversion) were reported as continuous variable (Mean ± SD or Median (25^{th}, 75^{th} percentile)) as recommended in earlier literature [26] and as categorical variables (with frequency of patients in 3 categories based on lesser, greater, no change between post- and pre levels).

Statistical analysis

In univariate analyses, order set and non-order set patient groups were compared for a significant difference in categorical variables using the Chi-square test (one or more variable categories had a frequency higher than five) or Fisher Exact test (one or more variable categories had frequency of five or less) as appropriate. The Bonferroni adjustment was applied to the p-values when three pairwise comparisons were arising from the three categories of these outcomes. Wilcoxon rank sum test was used to compute significant differences across the two groups (order set versus non- order set) for all continuous variables with non-normal distribution based on visual inspection of the histogram, skewness, kurtosis, and the Shapiro-Wilk test's W-statistic and p-values. Data analysis was performed using the Statistical Analysis System (SAS) software Version 9.4 for Windows (SAS Institute, Inc., Research Triangle Park, Cary, NC). All statistical tests were 2- tailed, and a p value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of 96 study eligible patients (with 37 in order set and 59 in the non-order set group as in **Appendix B**) after a retrospective chart review of 524 patients. There were no significant differences between the order set and the non-order set groups by age (median, 70 vs. 65 years, overall range 35-85 years), gender (males/females; 57%/43% vs. 53%/47%), history of diabetes prior to hospital admission (59% vs. 71%), and hospital length of stay (median; 15 vs. 16 days). Significantly more order set versus the non-order set group patients were Caucasians (84% vs. 59%, p=0.0135), had "cardiac-related" reason for admission (86% vs.59%, p=0.0016) and had a greater number of comorbidities (median number 8 vs. 6, p=0.0142). **Table 2** includes the four criteria for IV-SC insulin transition and IV and SC insulin doses in the order set and non-order set patients. The order set versus than the order set patients were significantly less likely to be on tube feed (19% vs. 58%) and concurrent steroid use (3% vs. 32%), respectively (p<0.05). Though not significantly different, more order set versus non-order set patients had an estimated GFR< 59 ml/min (that increases the risk for hypoglycemia) (62% vs. 49%) while fewer order set versus non-order set patients had a higher risk for hypoglycemia (38% vs. 51%). The hourly IV insulin dose and duration were significantly lower for the order set versus the non-order set group (median; dose, 2.0 vs. 2.5 units, p=0.026; duration, 39.48 vs. 60.07 hours, p=0.0015), respectively. The SC insulin doses over 24 hours were also significantly lower in the order set versus non-order set groups (median, 20 vs. 25 units, p=0.0058). Glargine versus Detemir was most frequently used long-acting acting SC insulin when patients were transitioned from IV insulin in both order set groups (used 76% vs. 24%; not used 54% vs. 46%).

Table 1. Characteristics of patients eligible for IV-SC Insulin conversion.

Characteristics (n, %; unless otherwise specified*)	Order set patients (n=37)	Non-order set patients (n=59)	P -Value
Age in years*	70 (61,75)	65 (59,72)	0.1262
Gender			0.8335
Male	21 (57%)	31 (53%)	
Female	16 (43%)	28 (47%)	
Race			0.0135¶
Caucasian	31 (84%)	35 (59%)	
Other**	6 (16%)	24 (41%)	
Reason for Admission			0.0016¶
Cardiac	32 (86%)	32 (54%)	
Non-Cardiac	5 (14%)	27 (46%)	
Number of Comorbidities*	8 (6,9)	6 (5,9)	0.0142¶
Hospital Length of Stay* (days)	15 (9,22)	16 (10,33)	0.1836
History of diabetes before hospital admission, Yes	22 (59%)	42 (71%)	0.2704

Note: *Median (25th, 75th percentile of median),
**Other race categories consist of Black, Oriental/Asian, American Indian, Spanish/Hispanic, and Pacific Islander/Hawaiian, and Unknown,
¶:Statistical significance at p </=0.05

Table 2. Association of criteria for IV-SC transition in automated conversion order set vs. non-order set patients

Criteria (n, % unless otherwise specified*)	Order set patients - (n=37)	Non-order set patients - (n=59)	P-value
Nutritional status			0.0003¶
PO	30 (81%)	25 (42%)	
TPN/Tube feed	7 (19%)	34 (58%)	
Steroid use (prednisone >10 mg)			0.0005¶
Yes	1 (3%)	20 (32%)	
No	36 (97%)	58 (68%)	
High risk of hypoglycemia < 70 mg/dL			0.2928
Yes	14 (38%)	30 (51%)	
No	23 (62%)	29 (49%)	
Estimated GFR			1.4853
<15 ml/min	1 (3%)	3 (5%)	
15 - 59 ml/min	13 (35%)	27 (46%)	
>59 ml/min	23 (62%)	29 (49%)	
Insulin infusion*			
Duration (hr)	39.48 (26.45, 60.63)	60.07 (41.95,149.25)	0.0015¶
Hourly insulin dose (units/hr)	2 (1.5, 2.5)	2.5 (2, 3)	0.0265¶
SC insulin			
Timing of SC Insulin within window			0.4647
Yes	10 (27%)	12 (20%)	
No	27 (73%)	47 (80%)	
Type of SC used			0.0507
Glargine (n, %)	28 (76%)	32 (54%)	
Detemir (n, %)	9 (24%)	35 (46%)	
SC Dose in units over 24 hr*	20 (10,28)	25 (18,48)	0.0058¶

Note: * Median (25^{th}, 75^{th} percentile of median),
SC: Subcutaneous, PO=Oral administration, TPN=Total Parental Nutrition, GFR=Glomerular Filtration Rate
¶: Statistically significant P<0.05

Table 3 describes the safety and clinical outcomes of IV-SC insulin transition in order set versus the non-order set groups. The safety outcomes (categorical variables) in order set versus non- order set patients were reported. First, the hypoglycemic events (percentage of patients with no change at 24 hours post- minus pre- IV-SC conversion; 86% vs. 85%, p>0.05),for the two groups were computed. Second, the hyperglycemic events at the 8-hour window (percentage of patients with more events at 24 hours post- minus pre- IV-SC conversion, 11% vs. 32%, p=0.0171) were calculated. The clinical outcome of blood glucose levels (categorical variable) showed minor fluctuations in the order set versus non-order set group (percentage of patients with less/more blood-glucose levels at 24 hours post- minus pre- IV-SC conversion, 43%/57% vs. 31%/69%, p=0.2747). Though not statistically different, the changes (post- minus pre- IV-SC transition increase) in blood-glucose levels were lower in order set patients versus non-order set patients (median 2.13 versus 15.46 mg/dL, p>0.05).

Table 3. Safety and clinical outcomes of IV-SC transition in automated conversion order set patients vs. non-order set patients.

Patient Outcome Characteristic [*n (%); unspecified Mean ± SD]	Order set patients - (n=37)	Non-order set patients	P-Value
Number of hypoglycemic events (<70 mg/dL) 24 hours			
Before IV-SC transition (pre-conversion)	0.05 ± 0.23	0.10 ± 0.30	0.4135
After IV-SC transition (post-conversion)	0.08 ± 0.28	0.05 ± 0.22	0.5535
Difference (post-conversion minus pre-conversion)	0.03 ± 0.37	(-) 0.05 ± 0.39	0.3321
Less*	2 (5%)	6 (10%)	2.0265
More*	3 (8%)	3 (5%)	
No difference*	32 (86%)	50 (85%)	
Number of hyperglycemic events (>180 mg/dL) 24 hours (3 hour window)			
Before IV-SC transition (3 hour window)	1.22 ± 1.29	1.81 ± 1.73	0.1256
After IV-SC transition (3 hour window)	1.11 ± 1.52	2.24 ± 1.95	0.0031¶
Difference (post-conversion minus pre-conversion)	(-) 0.11 ± 1.31	0.42 ± 2.18	0.2435
Less*	11 (30%)	19 (32%)	0.165
More*	9 (24%)	26 (44%)	

Table 3. Safety and clinical outcomes of IV-SC transition in automated conversion order set patients vs. non-order set patients (Continution).

No difference*	17 (46%)	14 (24%)	
Number of hyperglycemic events (>180 mg/dL) 24 (8 hour) window)			
Before IV-SC transition (8 hour window)	0.81 ± 0.94	1.05 ± 0.92	0.1816
After IV-SC transition (8 hour window)	0.59 ± 0.86	1.20 ± 0.98	0.002¶
Difference (post-conversion minus pre-conversion)	(-) 0.22 ± 0.82	0.15 ± 1.23	0.3342
Less*	8 (22%)	19 (32%)	0.0171¶¶
More*	4 (11%)	19 (32%)	
No difference*	25 (68%)	21 (36%)	
Average Blood-glucose levels (mg/dL) 24 hours			
Before IV-SC transition (pre-conversion)**	146.82 (130.82,152.95)	147.33 (140.61,162.31)	0.2868
After IV-SC transition (post-conversion)**	147.67 (129.46,167.00)	171.50 (143.53, 194.26)	0.0048¶
Difference in blood-glucose levels (post- conversion minus pre-conversion)**	2.13 (-12.10, 21.30)	15.46 (-2.54, 50.85)	0.3216
Less*	16 (43%)	18 (31%)	0.2747
More*	21 (57%)	40 (69%)	

Note: *n (%) unspecified Mean ± SD: Differences categorized as continuous and categorical variables,
**Median (25th, 75th percentile of median),
¶: statistically significant P<0.05,
¶¶: Bonferroni adjustment as 3 pairwise group comparisons

DISCUSSION

Earlier studies show that written protocols for IV-SC insulin transitions resulted in lower hyperglycemic and hypoglycemic events [5,6] yet, as per the Avanzini et al findings these reports are conflicting [6]. To the authors' knowledge, this is one of the first real-world retrospective cohort studies to evaluate the conversion via an automated order set, rather than via traditional written protocols. The study findings on safety and clinical outcomes support the hypothesis that the use versus non-use of automated order set was significantly associated with lower hyperglycemic events in a 8-hour window (post- minus pre- IV-SC insulin transition) (percentage of patients with more events, 11% vs.32%). Further, the differences in hypoglycemic events, and hyperglycemic events in a 3-hour window were not statistically significant across the order set versus the non-order set use patients, respectively (percentage of patients with more events after IV-SC transition in hypoglycemic events, 8% vs 5%; in hyperglycemic events in a 3 hour window, 24%vs.44%). Though not significant, the order set versus the non-order set use patients showed a lower average blood-glucose level post IV-SC conversion (median 147.67 vs.171.50 mg/dL). However, the study hospital protocol calls for a blood-glucose target range of 120-160 mg/dL, and the average blood-glucose for order set patients satisfied this criterion, while the non-order set patients did not. A related finding was that the average SC insulin dose after the IV-SC transition was significantly lower in the order set versus the non- order set group (20 vs. 25 median Units, U). The mean determir dose after the order set use, in particular, was lower than the non-order set patients (7.62 U versus 17.83 U, p=0.0244, data not shown in Tables). Future evaluations should investigate this difference in SC dose, as well as the potential cost savings from optimal lower use of SC insulin doses. The study findings perhaps do not show a clear advantage to the use of an automated order set; however, the finding of lower SC dosages in the order set versus the non-order set group along with the lesser likelihood of hyperglycemic and lower blood-glucose levels, imply that utilizing the order set may improve the efficiency of SC insulin usage. In summary, the study findings reported for the first time suggest that the automated order set helped eligible patients achieve better optimal glucose levels as per the study hospital protocol, with significantly lesser likelihood of hyperglycemia and at lower IV and SC insulin doses.

With regards to hospital criteria for order set use, the study found that order set patients versus non-order set patients were more significantly more likely to be on an oral diet and less likely to be on prednisone. It appears that the order set is being used for patients avoiding tube feeds and corticosteroid therapy; this finding is reported for the first time. Perhaps the reason for the greater incidence of hyperglycemic events in the non-order set group is because of prednisone's propensity to increase blood-glucose levels and potentially cause hyperglycemia [14]. Though additional supporting data is not available, future studies should investigate whether using the order set in patients who are on tube feeds and on steroids also reduces the likelihood for hyperglycemic events.

Another finding was that the order set patients were significantly more likely to be admitted for cardiac condition related reasons, and had a significantly greater number of comorbidities than the non-order set patient groups. It appears the order set

patients were more analogous than non- order set patients to the populations of similar insulin conversion studies, because of the greater percentage of cardiac patients [5-7]. This suggests that providers may perceive that the order set is primarily for cardiac patients. With only 64% of all study patients (data not shown) admitted for a cardiac reason, the overall study population had far greater heterogeneity of patients than other studies that focused primarily on cardiac patients [5-7].

A separate finding reported for the first time (not mentioned in majority of insulin conversion protocol studies) was that order set patients were significantly more likely to be Caucasian race than non-order set patients. Whether using the order set in patients of races other than Caucasian reduces the likelihood for hyperglycemic events needs future study. The order set and non-order set patients were comparable in having older patients (70 vs. 65-year olds), and similar to other insulin conversion protocol study patients with average age 67 years [5-7]. Though the order set and non-order set patients similarly had more males, overall, the study had fewer males (53-57%) than earlier compiled studies (67%) [5-7]. Further, race, age, and gender were not significantly associated with hyperglycemia in the current study ($p>0.05$, data not shown).

This study has several limitations. First, our patient data was reviewed retrospectively, so causation cannot be attributed to the findings and only association can be reported. Second, though statistical differences in percentage of patients reporting more hyperglycemic events within an 8-hour window are reported, the clinical significance of these findings on patient- reported outcomes need evaluation in future studies. Third, generalizing the results from this study to other hospitals with IV-SC insulin conversion protocols that differ from the one at the current study hospital must be done with caution. Fourth, study outcomes associated with the IV- SC transition, such as differences in hypoglycemia and average blood-glucose levels, were not found to be statistically significantly associated with the automated conversion order set use. The study estimates may have been because of the small sample size of the current study (though comparable to earlier studies with ~100 patients) [5-7].

The lack of data on the amount of rapid acting insulin could have affected the study estimates. Further, considering the small sample size, authors were unable to control for significant differences in patient characteristics and different uses of short-acting insulin that may have affected study estimates. Further, patients in the automated group that received less tube feeding may have received more bolus insulin for regular oral intake, which may have contributed to the lower rate of hyperglycemic events. However, authors were unable to corroborate this reasoning because of non-availability of data (BOLUS + basal insulin dose) on overall post transition insulin dose. Fifth, our study only embodied a 5 month period of time. This limited time span may not accurately reflect the outcomes over an extended length of time, whereas a study of longer duration may help focus on longer-term outcomes. However, the study authors were unable to analyze a larger population because only 5-month data were available after the implementation of the order set at the time of the study. From the current first baseline study, several of the limitations can be effectively addressed by studies in larger populations in the future.

With a keen focus on consistently improving patient safety, evaluations, such as the one this current study provides, will be utilized in our institution to facilitate discussions regarding improvement, and optimization of the current automated conversion order set. The results of this study will help in the modification of the current Critical Care Insulin Protocol to better implement the order set to suit patient needs. One such adjustment could be employing the automated conversion order set in a patient population beyond cardiac to include patients with a without a history of diabetes. The findings of this study can also serve as a useful tool for other hospitals seeking to implement similar practices, and to enhance the order set to improve patient outcomes. A cardinal area for future research would be evaluating the impact of the automated IV-SC insulin order set on SC insulin dosing efficiency and the subsequent potential cost savings this could offer hospitals.

CONCLUSIONS

Despite the small sample size, the study findings suggest that the eligible automated order set patients were associated with better optimal glucose levels as per study hospital protocol, with significantly lesser likelihood of hyperglycemia at lower IV-SC insulin doses. Providers and payers' future efforts are needed to implement and evaluate the impact of automated IV-SC insulin order set on SC insulin dosing efficiency and related potential cost savings in health care systems.

AUTHOR'S CONTRIBUTIONS

All authors conceived and designed the study. JS gained ethical approval. NT and JS got access to the data for the study. CM, AW, MP, KL carried out the data collection under the supervision of NT and JS. KL, MP, CM, and AW performed the analysis of the data under the supervision of JS. KL, MP, CM, and AW were involved in writing and revising the initial draft of the manuscript under the supervision of JS. All authors (KL, MP, CM, AW, and NT led by JS) had an opportunity to review and revise the final paper for intellectual content.

REFERENCES

1. Qaseem A, et al. Inpatient Glycemic Control: Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians. Am J Med Qual. 2014;29:95-98.
2. Bode B, et al. In-Hospital Management of Patients With Hyperglycemia: Transitioning From IV Insulin Therapy to Subcutaneous Insulin Regimens and Effective Discharge Planning to Maintain Glycemic Control (An Interactive Case Study). Medscape. 2007.
3. Umpierrez GE, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87:978-982.
4. Finfer S, et al. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. N Engl J Med. 2009;360:1283-1297.
5. Olansky L, et al. Cleveland clinic cardiovascular intensive care unit insulin conversion protocol. J Diabetes Sci Technol. 2009;3:478-486.
6. Avanzini M, et.al. Transition from intraveneous to subcutaneous insulin - effectiveness and safety of a standardized protocol and predictors of outcome in patients with acute coronary syndrome. Diabetes Care. 2011;34:1445-1450.
7. Stahnke A, et al. Pharmacy management of postoperative blood- glucose in open heart surgery patients: Evaluation of an IV-SC insulin protocol. Hosp Pharm. 2014;49:164-169.
8. www.ismp.org/tools/
9. Samaan KH, et al. Addressing safety concerns about U-500 insulin in a hospital setting. Am J Health Syst Pharm. 2011;68:63-68.
10. Aron A, et al. Subcutaneous versus intravenous insulin therapy for glucose control in non-diabetic trauma patients. A randomized controlled trial. J Clin Pharm Ther. 2013;38:24-30.
11. Moghissi ES, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32:1119-1131.
12. American Diabetes Association: Standards of medical care in diabetes-2012. Diabetes Care. 2012;35:S11-S63
13. Jacobi J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med. 2012;40:3251-3276.
14. Lavernia F. Treating Hyperglycemia and Diabetes With Insulin Therapy: Transition From Inpatient to Outpatient Care. Medscape. 2008.
15. Clement S, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27:553-591
16. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2008;31:S12-S54.
17. Goldberg PA, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. Diabetes Care. 2004;27:461-467.
18. Bode BW. Intravenous insulin infusion therapy: indications, methods, and transition to subcutaneous insulin therapy. Endocr Pract. 2004;10:71-80.
19. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc. 2004;79:992-1000.
20. Shetty S, et al. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale insulin infusion protocol. Endocr Pract. 2012;18:363-370.
21. Malmberg K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005;26:650-661.
22. American Association of Clinical Endocrinologists. The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management-2002 update. Endocr Pract. 2002;8:40-82.
23. Malmberg K. Role of insulin-glucose infusion in outcomes after acute myocardial infarction: the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study. Endocr Pract. 2004;10:13-16.
24. Tuttle KR, et al. Diabetic kidney disease: A report from an ADA consensus conference. Am J Kidney Dis. 2014;64:510-533.

25. Cavanaugh KL. Diabetes management issues for patients with chronic kidney disease. Clinical Diabetes. 2007;25;90-97.

26. Goldberg PA, et al. "Glucometrics" assessing the quality of inpatient glucose management. Diabetes Technol Ther. 2006;8:560-569.

Appendix A

Key elements of study hospital' critical care insulin protocol

The protocol is applied to include: all patients in critical care, PACU (post-anesthesia care unit) and step down units; excluding patients with DKA, HHS and/or pregnancy. Prescribers order through the IV Insulin Infusion Protocol when blood-glucose is greater or equal to 180 mg/dL on two successive occasions, or at the discretion of the prescriber.

The protocol includes a section on transitioning from IV insulin to subcutaneous insulin. The protocol specifies the dosing conversion of IV-SC based on factors such as: insulin drip rate (units/hour), nutritional intake status (total parenteral nutrition (TPN) or eating by mouth (PO)), prednisone intake and risk of hypoglycemia. The following patients require IV-SC transitioning with a particular type of insulin regimen:

- patients with Type 1 Diabetes Mellitus (DM), insulin-dependent Type 2 DM, or those patients requiring >1 unit/hour IV infusion should be provided with SC basal insulin (Glargine or Detemir) that should be administered at least 2 hours prior to stopping the insulin drip.
- In addition, patients who are eating should have a meal bolus of rapid acting insulin ordered and all patients should have a correction scale of rapid-acting insulin ordered to correct for hyperglycemia.
- How to calculate SC insulin doses for stable patients?
    - The average rate/hour for the patient's last 8 hours on the insulin drip is calculated then multiplied by 24 to get the total daily dose of insulin.
    - For patients who are eating, half of the total daily dose is given as long acting insulin (glargine or detemir). The remaining half of the dose is divided by 3 to determine the meal bolus dose of rapid acting insulin. Use insulin order sets to calculate correction scale for hyperglycemia for BG 140 mg/dL using the same rapid acting insulin.
    - For patients on tube feeds or TPN for basal insulin, calculate the average rate/hour for the patient's last 8 hours on the insulin drip as above. Then multiply the average rate/hour by 24 hours then by 0.75 to get the new total daily dose. Give 50% of new daily dose as basal long-acting insulin (glargine or detemir). The other approximate 50% of the new daily dose is to be given as boluses every 4 hour on a sliding scale. For bolus insulin, regular insulin may be added to the TPN bag.
    - For correction doses use insulin order sets to calculate correction scale for insulin lispro or insulin aspart (in the case of latex allergy) every 4 hours. If providers chose to use the order set when converting from IV to SC insulin they are prompted to complete a short automated checkbox list of options i.e. patient nutritional intake status (PO or TPN), prednisone dose (checked if >10mg/day), risk of hypoglycemia (checked if high risk), and eGFR. Based on this information in addition to previous IV drip rate and patient BMI, appropriate pre-calculated doses of long-acting and correction scale insulin are ordered.

Appendix B: Flowchart for identifying eligible hospitalized patients for the IV-SC insulin conversion protocol