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Use of a Subcutaneous Insulin Computerized GlucoStabilizer™ Program on Glycemic Control in the Intensive Care Setting: a Retrospective Data Analysis

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Abstract Background: Despite guidelines that recommend strongly against Sliding Scale Insulin (SSI) it continues to be the most commonly insulin regimen used in hospitals to treat hyperglycemia. In addition to being reactionary to a glucose that has already increased, SSI offers practical challenges in the randomness of the doses of insulin prescribed and often a disconnect with glucose testing that should be occurring in congruence to the insulin dosing. While many clinical trials have shown improved glycemic control in critical care patients receiving intravenous insulin; few studies have demonstrated the efficacy of subcutaneous (SQ) insulin in this setting. In this study, we have evaluated the safety and efficacy of SQ insulin administration utilizing a computerized program, the Clarian GlucoStabilizer™ Subcutaneous Program (CGS-SQ) in the intensive care unit (ICU). This program is designed to overcome some of the most common barriers of SQ insulin delivery, those of dose calculation and timing.

Methods: A computerized SQ insulin delivery program -The Clarian GlucoStabilizer™ Subcutaneous Program (CGS-SQ)- was made available to ICU practitioners, facilitating standardized calculation of insulin doses and incorporating reminder alarms for blood glucose (BG) testing. This program used three defaults Insulin Sensitivity Factors (ISF) and Insulin to Carbohydrate Ratios (CR) to calculate insulin doses. Additionally, there is an option for practitioner determined ISF and ICR. Patients, aged ≥ 18 years, initiated on the CGS-SQ and admitted to the (ICU) were eligible for inclusion in this retrospective evaluation. Patients were divided into four groups based on initial insulin sensitivity factor (ISF) and carbohydrate ratio (CR). Three of the groups used a default ISF and CR; ISF 60, CR 15; ISF 30, CR 10 and ISF 15, CR 8. These groups were compared with those where the practitioner specified an individualized ISF and CR, referred to as PDS (practitioner defined setting). Primary endpoints included: mean glucose, time to target glucose, hyperglycemic and hypoglycemic events.

Results: In the 1,384 patients identified, patients initiated with a predefined setting had lower mean glucose compared to patients with PDS (ISF 60, CR 15: 135 mg/dL vs. ISF 30, CR 10: 140 mg/dL vs. ISF 15, CR 8: 134 mg/dL vs. PDS: 143 mg/dL; p < 0.0001). Patients in the default settings had shorter time to target glucose and decreased incidence of hyperglycemia and hypoglycemia.

Conclusions: Using a system of computerized prompts with standardization of insulin dose calculation, SQ insulin can be effectively used in the treatment of ICU patients to target BG of 100-150 mg/dL with minimal risk of hypoglycemia.

Keywords Subcutaneous Insulin, Electronic, Critical Care

1. Introduction

Hyperglycemia in the critical care setting has shown to contribute to increased morbidity and mortality and can lead to multiple complications such as increased risk of infection, increased mechanical ventilation time, changes in hemodynamics, and changes in renal function [1, 2]. The American Association of Clinical Endocrinologists and American Diabetes Association therefore recommend control of hyperglycemia in critically ill patients with threshold glucose of ≥180 mg/dL [3]. This consensus committee statement also recommends frequent glucose

monitoring to decrease hypoglycemia while achieving glucose control [3] since hypoglycemia itself can also have deleterious effects on the patient.

Although many clinical trials have evaluated appropriate glucose goals in the ICU, controversy remains as to specific targets that would favor patient outcomes and decrease mortality in the critical care setting [4-5].Most studies evaluating the benefit of tight glucose control in the (ICU) have utilized intravenous (IV) insulin [3, 6-9]. We have published earlier, the results of our computerized Clarian GlucoStabilizer™ Intravenous Program (CGS-IV) demonstrating its effectiveness and safety in achieving and maintaining tight glucose targets in the ICU[10]. However, subcutaneous (SQ) insulin therapy continues to be used, primarily as sliding scale insulin (SSI)not only in non-ICU but also in critical care settings. In order to effectively control glucose with insulin therapy, three critical attributes need to be met: standardization of insulin dose calculation, timely checking of BG, and standardized insulin dose readjustment. If one or more of these attributes are not met, the potential for persistent hyperglycemiaor development of hypoglycemiamay result. Appropriate protocol selection and implementation therefore is vital to the success of any glucose management strategy.

Following the demonstrated safety and efficacy of the CGS-IV program, we sought solutions to the challenges we were encountering in SQ insulin delivery. Paper Protocols promoting basal bolus insulin were introduced and were modestly successful. There continued to be a demand for a more standardized solution to calculate and administer SQ insulin within the hospital system. In 2006, Clarian Health, now Indiana University Health (IUH), launched the Clarian GlucoStabilizer™ Subcutaneous Program (CGS-SQ), to meet this need. This is a computerized program developed to standardize SQ insulin administration and reduce calculation errors [11].The program can be used to recommend most aspects of SQ insulin dosing including individual: prandial insulin doses, correction insulin doses, and treatment for hypoglycemia. The program is initiated by the practitioner, and enhances compliance with audible and visual reminder alarms for glucose testing [11]. Each insulin dose is administered SQ by the patient's nurse, in response to prompts from the program. The CGS-SQ has traditionally been utilized in non-critically ill patients; however, in recent years the program has also found acceptance inthe ICU. The objective of this study was to evaluate the efficacy and safety of the Clarian SQ GlucoStabilizer on glycemic control in the ICU.

2. Methods

This study is a retrospective data analysis evaluating the efficacy and safety of SQ insulin administration utilizing the CGS-SQ on glycemic control in the ICU. The study included data collected at two large academic medical centers, University Hospital (UH) and Methodist Hospital (MH) in Indianapolis, Indiana from January 1, 2009 to June 30, 2009.

Details of the CGS –SQ has been described elsewhere [11]. Briefly, once the practitioner orders SQ insulin via a standardized order set, the nurse initiates the computerized program. The program utilizes insulin sensitivity factors (ISF), carbohydrate ratios (CR), and blood glucose (BG) testing every three hours orevery four hours to facilitate rapid-acting insulin dose calculation and administration. ISF is the estimated reduction in BG that would occur with one unit of rapid-acting insulin. CR is the estimated number of grams of carbohydrate covered by one unit of rapid-acting insulin. The practitioner can use one of the available default settings for these parameters (ISF 60, CR 15; ISF 30, CR 10 and ISF 15, CR 8). These default settings are based on body weight and were decided upon based on a consensus of physicians, pharmacists and nurses with experience in inpatient hyperglycemia management. If a patient weighs less than 68 kg the default setting is an ISF 60, CR 15 and if 68 kg or greater an ISF 30, CR 10 is the default. An ISF 15, CR 8 setting is also available and can be chosen by the treating practitioner based on the patient's perceived insulin needs. In addition, the treating practitioner has the ability to customize practitioner defined settings (PDS) for ISF or CR. The nurse enters the selected parameters into the software along with the starting BG value and the program clock is initiated. Glucose is tested every 3 or 4 hours, depending on the order set used.At MH, the order set utilizes 3 hour glucose testing while at UH a 4 hour glucose testing frequency is the default. The timings of 3 or 4 hours for glucose testing were based on a consensus similar to the ISF and CR calculations. In addition the program sets a default BG target range of 100-150 mg /dL and the ISF is designed to target to the mid-point of this target range. Practitioners are able to modify the target range to suit their patient's particular needs.

When the program alarm (visual and audible) initiates for glucose testing, the treating nurse uses a point of care device to obtain a glucose reading, which is entered into the computer program. The program then determines the amount of insulin to be administered based on the patient's glucose reading, target glucose range, ISF, and CR. For prandial insulin dosing, the program calculates a dose of rapid-acting insulin utilizing the total number of grams of carbohydrate consumed in the meal or bolus tube feeding. For correction insulin dosing, the program calculates a dose of rapid-acting insulin based on the current BG and the midpoint of the target range using the ISF. Hypoglycemia recovery instructions include a standardized dose of dextrose 50% or grams of oral carbohydrates to be administered followed by BG testing every 15 minutes until the BG is ≥ 70 mg/dL. Numerous safeguards are built into the software such as alerts for potentially unsafe insulin doses and criteria for calling the practitioner [11].Guidelines for basal insulin administration are not part of the current version of the software; this insulin is administered separately based on practitioner instructions.

In this study, comparison of initial ISF, CR, and frequency of glucose testing were evaluated to determine the most

appropriate initial program settings. Patients were identified through the CGS-SQ database along with the hospital patient database. All adult patients, 18 years of age or older, admitted to an ICU and initiated on the CGS-SQ program were screened but data was only analyzed for those patients in whom the practitioner had selected a target BG range of 100-150 mg/dL which was standard of care at MH and UH during the study period. Patients were excluded if they received IV insulin while in the ICU. This study included a mixed ICU population including: medical, surgical, cardiovascular, trauma, neurosurgical, pulmonary, bone marrow transplant, and solid organ transplant patients.

Patients were categorized into one of four groups based on initial ISF and CR settings. Patients either had one of three predefined ISF and CR settings (ISF 60, CR 15; ISF 30, CR 10; ISF 15, CR 8) or PDS for ISF and CR.

The primary endpoints included: time to target glucose range, time in target glucose range, mean ICU glucose, hyperglycemic events, hypoglycemic events, and frequency of glucose testing. To evaluate hyperglycemic events, blood glucose values were studied in intervals of 10 mg/dL starting at $\geq$ 150 mg/dL to $\geq$ 250 mg/dL. Hypoglycemic events were also studied at decrements of 10 mg/dL starting at $\leq$ 70 mg/dL to $\leq$ 40 mg/dL.

2.1. Statistical Analysis

Time in target glucose range and mean glucose were compared between the four treatment groups using ANOVA while hyperglycemic and hypoglycemic events were analyzed using Chi-Square analysis. The time to achieving target glucose range in each group was compared using Mantel-Cox analysis. A p-value of < 0.05 was established as statistically significant.

3. Results

During the 6 month study period, 1,384 patients met the inclusion criteria. A total of 34,514 blood glucose measurements were recorded. Seven hundred seventy-one patients (56%) had initial blood glucose readings outside their target glucose range (100-150 mg/dl); in the remainder, the program was initiated by the practitioner presumably to keep BG in target of 100-150 mg/dl during the ICU stay. For those patients with initial BG outside the target range at program initiation, the mean admission glucose was 174.1 ± 62.2 mg/dL and the mean time to achieving the target of 100-150 mg/dl was 18.5 ± 1.37 hours (median 9.23 ± 0.43 hours). The mean glucose after achieving target was 137 ± 28.7 mg/dL. For those in the target range on admission, the mean admission glucose was 126.1 ± 14.0 mg/dL and the mean glucose while in the ICU was 131.8 ± 26.1 mg/dL. Patients initiated with one of the predefined settings had a shorter time to achieving the target glucose range compared to practitioner defined settings (Table 1). Patients in the ISF 15, CR 8 group had the shortest mean time to target range of 11.2 hours (median 6.9 hours). Overall, 81 patients (10.5%) did notachieve the target range of 100-150 mg/dl during their treatment in the ICU with the CGS-SQ.

Patients initiated with one of the predefined settings spent more time within the target glucose range (ISF 60, CR 15: 52% vs. ISF 30, CR 10: 46% vs. ISF 15, CR 8: 54 % vs. PDS: 40%; p < 0.0001 Table 1). In addition, mean glucose within the default groups was lower than the PDS group (ISF 60, CR 15: 135 mg/dL vs. ISF 30, CR 10: 140 mg/dL vs. ISF 15, CR 8: 134 mg/dL vs. PDS: 143 mg/dL; p < 0.01).

Table 1. Target Glucose Attainment

	ISF 60, CR 15 (n=106)	ISF 30, CR10 (n=374)	ISF 15, CR 8 (n=193)	PDS (n=98)	p-value
Patients initially out of range who reached target	98 (92%)	322 (86%)	182 (94%)	88 (90%)	[*]p<0.001
Median time to target range 100-150 mg/dL (hrs)	11.1	10.1	6.9	14.5	[*]p<0.001
Time in range	52%	46%	54%	40%	[†]p<0.01

[*]Comparison between all groups
[†] Each group compared to PDS

The frequency of hyperglycemia was evaluated in all patients, including those initially within the target BG range and those initially outside of the target BG range. Evaluation started at measurements of blood glucose $\geq$ 150 mg/dL and then in 10 mg/dL increments up to $\geq$ 250 mg/dL. The overall frequency of hyperglycemia (BG $\geq$150 mg/dL) was 24.5% (n=8,442 BG measurements). Patients initiated with one of the default settings had fewer hyperglycemic events compared to practitioner initiated settings (Table 2). The ISF 15, CR 8 group had the fewest hyperglycemic events with 21.4% of measurements being $\geq$ 150 mg/dL and 0.8% being $\geq$ 250 mg/dL.

The frequency of hypoglycemia was also evaluated in all patients. Measurements were evaluated starting at a blood glucose of $\leq$ 70 mg/dL and then in 10 mg/dL decrements down to severe hypoglycemia of $\leq$ 40 mg/dL. The overall incidence of hypoglycemia (BG $\leq$ 70 mg/dL) was low at 1.1% (n=368/34,514 BG measurements). Patients initiated with one of the

default settings had a lower incidence of hypoglycemia compared to PDS settings (Table 2). The incidence of severe hypoglycemia (BG $\leq$ 40 mg/dL) was extremely low (0.1% of all readings) (Table 2). On a per patient basis, patients with PDS experienced more hypoglycemia 0.38 events/patient (Table 3).

Table 2.　Blood Glucose Measurements

	ISF 60, CR 15 (n=191)	ISF 30, CR 10 (n=656)	ISF 15, CR 8 (n=374)	PDS (n=163)	[*]p-value
Hypoglycemia					
Measurements $\leq$ 70 mg/dL	0.9%	0.9%	1.2%	1.3%	NS
Measurements $\leq$ 60 mg/dL	0.3%	0.3%	0.5%	0.6%	NS
Measurements $\leq$ 50 mg/dL	0.1%	0.1%	0.2%	0.1%	NS
Measurements $\leq$ 40 mg/dL	0%	0%	0.1%	0%	NS
Hyperglycemia					
Measurements $\geq$ 150 mg/dL	22.7%	26.5%	21.4%	29.7%	p<0.01
Measurements $\geq$ 160 mg/dL	17.4%	20.2%	15.2%	23.1%	p<0.01
Measurements $\geq$ 170 mg/dL	13.4%	15.2%	10.7%	18.6%	p<0.01
Measurements $\geq$ 180 mg/dL	9.6%	11.5%	7.4%	14.3%	p<0.01
Measurements $\geq$ 190 mg/dL	7.3%	8.9%	5.1%	11.4%	p<0.01
Measurements $\geq$ 200 mg/dL	5.6%	6.9%	3.6%	9.3%	p<0.01
Measurements $\geq$ 210 mg/dL	4.2%	5.2%	2.6%	7.3%	p<0.01
Measurements $\geq$ 220 mg/dL	3.2%	4.1%	2.0%	6.2%	p<0.01
Measurements $\geq$ 230 mg/dL	2.4%	3.1%	1.5%	4.8%	p<0.01
Measurements $\geq$ 240 mg/dL	1.8%	2.5%	1.1%	3.9%	p<0.01
Measurements $\geq$ 250 mg/dL	1.4%	2.0%	0.8%	3.1%	p<0.01

[*]Each default setting compared to the PDS group
NS = not significant

Table 3.　Hypoglycemic Events

	ISF 60, CR 15 (n=191)	ISF 30, CR 10 (n=656)	ISF 15, CR 8 (n=374)	PDS (n=163)	p-value
Patients with hypoglycemia (BG $\leq$ 70 mg/dL)	11%	9%	15%	19%	[*]p<0.01
Mean episodes of hypoglycemia per patient	0.21	0.20	0.36	0.38	[†]p<0.01
Total number of hypoglycemic events (BG $\leq$ 70 mg/dL)	40	131	135	62	--

[*]ISF 30, CR 10 compared to PDS. No difference found between other groups.
[†]ISF 60, CR 15 and ISF 30, CR 10 compared to PDS. No difference found between other groups.

The relationship of frequency of glucose testing to the efficacy and safety of the program was also evaluated. Patients who had every 3 hour glucose testing, irrespective of ISF or CR settings, had a shorter time to target glucose range, more time spent within the target glucose range, lower mean glucose, and decreased frequency of hyperglycemia (Table 4).

Table 4. Frequency of Glucose Testing

	Every 3 hours	Every 4 hours	PDS	*p-value
Time to target range (hrs)	10.5	17.4	22.2	p<0.01
% of time in target range	57%	52%	32%	p<0.01
Mean glucose (mg/dL)	132 ± 34	137 ± 39	149 ± 52	p<0.01
Measurements ≥ 150 mg/dL	19.5%	24.6%	32.9%	p<0.01
Measurements ≤ 70 mg/dL	1.1%	1%	1.4%	NS

*Comparison between every 3 hours and every 4 hours compared to PDS
NS = not significant

4. Discussion

Subcutaneous insulin delivery in the hospital has its challenges but is still the preferred route of insulin delivery. The first challenge is effectively getting patients within a preset glucose target. Our data shows that with the Clarian SQ GlucoStabilizer (CGS-SQ) mean time to target of 100-150 mg/dl was 18.5 hours (median 9.2 hours), percentage of hyperglycemic BG readings (≥ 150 mg/dL) 24.5%, and mean BG after target achieved 137 ± 28 mg/dL. When we compare this to our efficacy outcomes of the Clarian IV GlucoStabilizer, the mean time to target of 80-110 mg/dLwas 6.9 hours (median 6 hours); percentage of hyperglycemic BG readings (≥150 mg/dL) 8.0 %; and mean BG after target achieved 98.1 mg/dL [10]. When comparing the two programs, it is important to note differences in goal blood glucose ranges and insulin administration. However, if we look individually at each ISF and CR setting, it differs; for example, the mean for ISF 15, CR 8 mean time to target was only 11 hours. These data suggest that both the IV and SQ CGS programs are efficacious in correcting BG in critically ill patients.

Regarding safety, the CGS-IV resulted in 3.5% of the BG readings ≤ 70 mg/dL, while only 0.4% were ≤ 50 mg/dL. The hypoglycemic events for the CGS-SQ were 1% ≤ 70 mg/dL, 0.4% ≤ 60 mg/dl, 0.1% ≤ 50mg/dL and only 0.04% ≤ 40 mg/dL. These data suggest that although there is a greater risk of hypoglycemia with IV insulin, the risk of severe, life threatening hypoglycemia is not different in the ICU when computerized IV or SQ insulin dosing tools are used.

The target BG used in our institution with the CGS-SQ was far more stringent than those recommended by the AACE/ADA consensus panel [3], in whose opinion a BG range of 140-180 mg/dL is more acceptable for most institutions.Amongst the concerns that led the consensus panel [3] to raise their recommended targets from the earlier 80-110 mg/dL were the potential for increase in mortality thought to be contributed, at least in part, by the risk of hypoglycemia when trying to achieve tight glucose control. Our data earlier with the CGS-IV [10], and now with the CGS-SQ, however clearly demonstrates that tighter glucose control can be achieved with minimal risk of hypoglycemia in the critically ill patient, if one uses computer driven insulin administration algorithms.

Our study does have limitations. It is a retrospective evaluation of data, and not a randomized controlled trial. However, this is an analysis of data from a real world ICU setting where treating practitioners were making the clinical decision to use SQ insulin for their patients. The CGS-SQ is a computerized tool that offered them a means to standardize dose calculations and, after initiation, ensure compliance in insulin delivery and glucose testing. In addition to standardization, the computerized program offers additional advantages over a paper based SSI insulin regimen, assisting in nursing reminders and hypoglycemia protocols. As such,this meaningful analysis is able to demonstrate that when treating practitioners use a computer program, safe and effective SQ insulin delivery is possible even in the ICU.

Another potential limitation is documentation of basal insulin administration. Because of the limitations within our data collection software, we were not able to determine which of the patients included in our study received basal insulin. Anecdotally, however, we know that the vast majority of the patients in our institution are treated with both basal and bolus insulin regimens.Lastly, although the study was conducted in two different hospitals, both hospitals belong to the same health care system with a sharing of resources and staff. There is long standing glycemic control initiative in these institutions; the Systematic Utilization of Glucose Assessment and Response (SUGAR™) Program [11-13] with heightened awareness towards insulin treatment and aggressive monitoring of BG which could have influenced the results. However, part of the reason for the heightened awareness is the CGS programs themselves and their associated alarm functions which facilitate better care. Having the study repeated therefore in other institutions where such a heightened awareness does not exist may be of benefit.

Irrespective of targets for glucose control, insulin is the only safe and recommended means of managing hospital hyperglycemia [3]. This drug however continues to remain a high-alert medication and therefore standardization of insulin delivery is of paramount importance [14]. Our data show the reminder systems and standardized dosage calculations, integral to the software of the CGS-SQ, provide

a safe and effective means for reducing insulin administration errors. Given that over 35% of the patients being admitted to the hospital manifest hyperglycemia [15] it is imperative that we have safe and effective insulin delivery systems for the practitioners to use. The CGS-SQ has been shown to be safe and effective now, not only in the non-critically ill [11] but also in the treatment of the ICU patient.

5. Conclusion

The mainstay treatment of hyperglycemia in the ICU has always been IV insulin which is a very labor intensive process. The Clarian GlucoStabilizer (CGS-SQ) is the first software program that has evaluated the effectiveness of SQ insulin in the treatment of the critically ill patient. Our study has shown that by using a system of computerized prompts with standardization of insulin dose calculation and reminder alarms, SQ insulin can be effectively used in the treatment of ICU patients to target BG of 100-150 mg/dL with minimal risk of hypoglycemia.

This study offers a critical insight into the safety and effectiveness of SQ insulin use in the ICU. Data from this analysis demonstrates the CGS-SQ can be used to design future randomized clinical trials, where the variability created by different insulin protocols can be minimized allowing for a true testing of the hypothesis of the effectiveness of tight glucose control and its effects on outcomes of morbidity and mortality in the critically ill patient.

6. Key Messages

• Hyperglycemia in the critical care setting has shown to contribute to increased morbidity and mortality and canlead to multiple complications.

• The Clarian GlucoStabilizer™ Subcutaneous Program is a computer program utilizing insulin sensitivity factors, carbohydrate ratios, and every three or four hour blood glucose testing to facilitate rapid-acting insulin dose calculation and administration.

• In our current study, the Clarian GlucoStabilizer™ Subcutaneous Program resulted in a mean blood glucose of 137 mg/dL with a median time to target glucose range of 9.2 hours.

• Using a system of computerized prompts with standardization of insulin dose calculation, subcutaneous insulin can be effectively used in the treatment of ICU patients to target blood glucose of 100-150 mg/dL with minimal risk of hypoglycemia.

Acknowledgements

Competing Interests

Dr. Samuel Flanders and Dr. Rattan Juneja receive royalties from the commercial sales of the Clarian GlucoStabilizer software. Dr. Rattan Juneja is a consultant for Sanofiand Roche and Speaker for Eli Lilly, BoehringerIngelheim, Janssen, Merck and Bristol Myers Squibb. All other authors declare that no competing interests exist.

Glossary

BG= Blood Glucose, CGS-SQ=Clarian GlucoStabilizer™ Subcutaneous Program, CR = Insulin to Carbohydrate Ratio, ISF = Insulin Sensitivity Factor, PDS = Practitioner Defined Settings, SSI = Sliding Scale Insulin, SQ= Subcutaneous Insulin

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