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HOSPITAL MANAGEMENT OF DIABETES (A WALLIA AND J SELEY, SECTION EDITORS)

Review of Intravenous and Subcutaneous Electronic Glucose Management Systems for Inpatient Glycemic Control

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Abstract

Purpose of Review The goal of this review is to summarize current literature on electronic glucose management systems (eGMS) and discuss their benefits and disadvantages in the inpatient setting.

Recent Findings We review different versions of commercially available eGMS: Glucommander™ (Glytec, Greenville, SC), EndoTool^{R} (MD Scientific LLC, Charlotte, NC), GlucoStabilizer™ (Medical Decision Network, Charlottesville, VA), GlucoCare™ (Pronia Medical Systems, KY), and discuss advantages such as reducing rates of hypoglycemia, hyperglycemia, and glycemic variability. In addition, eCGMs offer a uniform standard of care and may improve workflows across institutions as well reduce barriers.

Summary Despite ample literature on intravenous (IV) versions of eGMS, there is little published research on subcutaneous (SQ) insulin guidance. Although use of eGMS requires extensive training and institution-wide adoption, time spent on diabetes management is better facilitated by their use.

Keywords Electronic glucose management system · Inpatient diabetes management · Glucommander™ · EndoTool^{R} · GlucoStabilizer™ · GlucoCare™

Introduction

Current guidelines for inpatient glycemic management outcomes recommend a blood glucose target of 140–180 mg/dL (7.8–10 mmol/L) in most critically ill and noncritically ill patients. A more stringent blood glucose target of 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for select patients if this can be achieved without significant hypoglycemia [1]. Professional societies such as the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend the use of basal/bolus insulin therapy for patients with hyperglycemia in non-critical care settings and intravenous insulin infusions based on validated written or computerized protocols in critical care settings. There is substantial evidence linking hyperglycemia in hospitalized patients (with and without diabetes) to poor outcomes [2]. Despite this, there are challenges to achieving optimal inpatient glycemic targets due to fluctuations in inpatient clinical factors, dietary changes, institutional variability in expertise/education in diabetes care, clinical inertia, and fear of hypoglycemia. Electronic glucose management system (eGMS) is a possible solution to overcome these obstacles.

Historically, a 2001 randomized clinical trial from Van den Berghe et al. showed that intensive glucose management (target 80–110 mg/dL) in critically ill surgical intensive care unit (SICU) patients led to reduction in morbidity and mortality compared to permissive hyperglycemia [3]. Subsequent studies, however, like the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, found that targeting BG 81–108 versus intermediate target < 180 m/dL was associated with high rates of moderate and severe hypoglycemia and increased all-

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cause mortality [4]. Hypoglycemia has been well established as an independent risk factor for mortality in the intensive care unit (ICU) setting [5, 6]. Glycemic variability also portends increased risk for ICU and hospital mortality, even more than hypoglycemia alone [7, 8]. With the advent of commercial eGMS, benefits, such as longer maintenance of glucoses in tighter target ranges, quicker time to target ranges, lower glycemic variability, fewer calculation errors, built-in alert systems, and easier data analysis, have led to advancement in inpatient diabetes care without the negative impacts of hypoglycemia seen in the NICE-SUGAR study. Despite this, their higher costs, maintenance fees, and technical support requirements have limited penetration of eGMS in healthcare. We review current literature on the four Food and Drug Administration (FDA)-approved, commercially available eGMs: Glucommander™ (Glytec, Greenville, SC), EndoTool^{R} (MD Scientific LLC, Charlotte, NC), GlucoStabilizer™ (Medical Decision Network, Charlottesville, VA), GlucoCare™ (Pronia Medical Systems, KY), and briefly delve into institutionally grown computerized clinical decision support tools.

Benefits of Electronic Glucose Management Systems

Glucommander™

Glucommander™, a FDA-cleared and health insurance portability and accountability act (HIPAA) compliant, cloud-based software system, is dedicated to use in the inpatient setting. It can be integrated directly into the electronic health record (EHR) and is available to automate insulin delivery in intravenous (IV), subcutaneous (SQ), transition, pediatric IV, and outpatient versions (Table 1). Its proprietary multiplier-model-based controller calculates hourly rates for the IV version via the equation (insulin/hour = multiplier × (blood glucose − 60)). The multiplier or insulin sensitivity factor (ISF) is auto-adjusted to reach target blood glucose ranges. It was originally derived from the data presented by White et al. in a 1982 article on a closed loop insulin delivery system [9].

Although first developed in 1984, the first paper on Glucommander's benefits was published in Diabetes Care by its creators in 2005 [10]. They found that out of 5080 runs using the software in multiple different ICU and non-ICU units, only 2.6% of the runs had glucose levels less than 40 mg/dL, which was less than the hypoglycemia rates in the Van den Berghe study in 2001 (5.2%) [3]. Mean blood glucose (BG) levels ≤ 150 mg/dL was reached within 3 h of use, and only 0.6% of glucose values were less than 60 mg/dL. This formal introduction of Glucommander paved the way for its expansion into other institutional milieus, which began replicating an array of studies. A randomized controlled trial of medical ICU patients in four academic centers in Atlanta, GA, demonstrated that the Glucommander group experienced lower mean BG (103 ± 8.8 versus 117 ± 16 mg/dL; $P < 0.001$), shorter time to reach BG target of 80–120 mg/dL (4.8 ± 2.8 versus 7.8 ± 9.1 h, $P < 0.001$), higher percent time in range (71.1 versus 51.3%, $P < 0.001$), with no difference in hypoglycemia compared to paper protocol [11]. Another smaller study at an academic medical center looking at Glucommander IV in medical and surgical ICUs showed that in critically ill, non-diabetic ketoacidosis (DKA) patients, percentage of days with BG < 70 mg/dL was greatly reduced after implementation of eGMS (1.3 versus 21.5%; $P < 0.0001$), with reduction of severe hypoglycemia days < 40 mg/dL (0.01 versus 5.4%; $P < 0.0001$). Patients in the eGMS group also spent greater time in target BG range of 110–180 mg/dL (63.7 versus 31.5%; $P < 0.0001$) and had lower glycemic variability (26.56 versus 49.27%, $P = 0.001$) [12].

There have been several studies dedicated to Glucommander's effectiveness in managing DKA. The earliest was a small study with no control arm, conducted at a community hospital with 35 emergency department (ED) patients with DKA [13]. The authors concluded that Glucommander patients reached BG target set by the admitting ED provider in 5 h and 11 min along with low rates of hypoglycemia with no episodes of severe hypoglycemia < 40 mg/dL. Of these 35 patients, 16 were discharged home directly from the ED and 19 were admitted, saving the hospital $78,000 for the non-admissions. Only one out of 16 patients discharged from the ED was admitted within 30 days. A larger multicenter, retrospective study spanning 2 years also compared Glucommander IV to a paper-based protocol for treatment of patients > 18 years of age, admitted with DKA to ICU and step-down units [14]. Results demonstrated that resolution of DKA was faster in the Glucommander group (9.7 ± 8.9 h) compared to the paper-based infusion (19.6 ± 18.7 h; $P < 0.001$) and length of stay (LOS) was also shorter (3.2 ± 2.9 versus 4.5 ± 4.8 days; $P = 0.01$). Percent of patients with hypoglycemia was also lower for Glucommander (BG < 70 mg/dL, 12.9% versus 35%; $P = 0.001$) (BG < 40 mg/dL 0.46 versus 6.6%, no P value reported). Both studies show that Glucommander is safe and effective for use in DKA management. Given that the annual national aggregate cost of DKA hospitalizations increased from 2.2 billion US dollars in 2003 to 5.1 billion US dollars in 2014 [15], using eGMS to shorten DKA management could translate into significant cost savings.

Glucommander has also been studied in cardiac populations. The Randomized Controlled Trial of Intensive versus Conservative Glucose Control in Patients Undergoing Coronary Artery Bypass Graft Surgery (GLUCO-CABG) trial is an outcomes trial using Glucommander IV in both intensive (100–140 mg/dL) and conservative management (140–180 mg/dL) arms containing CABG patients with and without

Table 1 Comparison of the different eGMS

eGMS	Company	Integration/mathematics	Versions	Other perks	Treatment of Hypoglycemia	Time to target	Hypoglycemia incidence (Percent of BG readings)
Glucommander™	Glytec, Greeville, SC	Cloud-based (GlyCloud^{R}) HIPAA compliant, and EHR integrated with bidirectional HL7 interface between the system and the patient chart without need for additional hard drive PID; linear formula for mathematics with sensitivity factor/multiplier	IV, SQ, transition, outpatient, pediatric IV	GlucoSurveillance^{R} to locate uncontrolled patients; GlucoView^{R} for alerts; SmartClick^{R} for single sign on from EHR and to upload POC glucoses from chart; GlucoMetrics^{R} for analysis of all glycemic data with one click; H2H^{R} hospital to home system for discharge regimen	Built-in as a protocol into the software. Glucose treatment formula: 50% BG level = (100−BG) × 0.2 g	Variable based on target: 3 h[11] 4.8 h[12]	IV: < 70 mg/dL = 0.9%[22], 1.3%[13] < 40 mg/dL = 0.001%[13] < 50 mg/dL = 0.6% (no severe hypoglycemia)[11] SQ: < 70 mg/dL = 1.74%[25], 1.9%[24] <40 mg/dL = 0.11%[25], 0.06%[24]
EndoTool^{R}	MD Scientific LLC, Charlotte, NC	Direct EHR integration via HL7 interface without additional hard drive. HIPAA compliant MPC controller: complicated algorithm of dosing relying on 11–13 physiological parameters and quadratic dosing curve	IV, SQ, transition, pediatrics (at least 2 years and 12 kg)	Estimated Residual Extracellular Insulin (EREI) to estimate insulin on board; optional EndoX mode to assist with DKA and/or HHS; EndoTool Analytics: to analyze organizational trends and to share metrics	Built into the system to trigger at a pre-selected low glucose value	1.5–2.3 h to reach < 180 mg/dL[29]	IV: < 70 mg/dL = 0.93%[29] < 40 mg/dL = 0.03%[29], 0.05%[27] SQ not evaluated in literature
GlucoStabilizer™	Medical Decision Network, Charlottesville, VA	Uses supervised secure intranet within hospital system and integrates to EHR via HL7 interface. HIPAA compliant PID; Linear formula for mathematics with sensitivity factor/multiplier	IV, SQ, pediatrics	No other analytics reported on website	Built into the system with formula for dextrose [(100 − BG) × 0.4 g)]	3.84 h to achieve BG < 170 mg/dL (2015 metrics on website); 3.8 ± 2.8 h to reach 95–135 mg/dL[35]	IV per website: < 70 mg/dL = 0.25% < 40 mg/dL = 0.015% IV literature reported: < 70 mg/dL = 1.36%[33], 0.51%[35] < 40 mg/dL = 0.1%[33], 0.14%[35] SQ: < 40 mg/dL = 0.18%[39]
GlucoCare™	Pronia Medical Systems, KY	Yale protocol-based software. HIPAA compliant. Runs cloud-based or on common web browsers via hospital intranet. No additional hardware PID linear formula	IV, IV to SQ transition	Analytics embedded into the system for quality improvement. Customizable targets: 140(B); 160 mg/dL target And various ranges: 100–140 mg/dL, 90–120 mg/dL, 120-140 mg/dL; 140–160 mg/dL	Recommendation provided	4.3 h on average to achieve 100-140 mg/dL[41]	IV per website: < 70 mg/dL = < 0.2% IV literature reported: < 70 mg/dL = 1.13%[41], 0.04%[42] for 140B protocol < 40 mg/dL = 0.01%[41]

BG, blood glucose; *DKA*, diabetic ketoacidosis; *EHR*, electronic health record; *HHS*, hyperosmolar hyperglycemic state; *HIPAA*, health insurance portability and accountability act; *HL-7*, health level 7; *IV*, intravenous; *MPC*, model predictive control; *PID*, proportional integral derivative; *POC*, point of care; *SQ*, subcutaneous

diabetes [16]. Although there were no differences in the diabetes subgroup, intensive glucose management with Glucommander in the non-diabetes subgroup led to reduction of peri-operative complication rates (34 versus 55%; $P = 0.008$). Hypoglycemia < 70 mg/dL occurred in more patients in the intensive group compared to conservative group (8 versus 3%, $P = 0.13$), but there were no cases of severe hypoglycemia < 40 mg/dL. Post hoc analysis of GLUCO-CABG trial data looking predominantly at cost analysis demonstrated lower hospitalization costs in the intensive treatment group ($36,682 versus $40,913, $P = 0.04$) with average cost savings of $3654 per case. Resource utilization (labs, radiology, ICU use, consultations) was also lower in the intensive treatment group [17]. Diabetes is a costly public health crisis, and global health expenditure are reported to be 760 billion US dollars in 2019 [18]. Further retrospective analysis comparing GLUCO-CABG to paper-driven infusion protocols in CABG patients could determine if there are non-glycemic benefits imparted by use of eGMS over paper protocols.

Glucommander has also been studied in special inpatient populations, including bone marrow transplant (BMT) recipients. BMT patients have high rates of non-relapse mortality (NRM) at 3 years after allogenic hematopoietic cell transplant (HCT). Prior studies have shown that hyperglycemia, hypoglycemia, and glycemic variability are associated with increased day 200 NRM, infections, and graft versus host disease (GvHD) [19, 20]. A 2016 study evaluated the use of Glucommander IV on 19 patients after allogenic HCT [21]. Ninety percent of these patients were on high-dose steroids for GvHD, and close to 50% on total parenteral nutrition (TPN). Patients using Glucommander reached target of 100–140 mg/dL after median of 6 h and remained in target 61% of the time (versus 0.58% and 20.95% before and after Glucommander). Hypoglycemia < 70 mg/dL occurred only for 0.9% of BG readings with no readings below 51 mg/dL. This study demonstrates that eGMS can achieve stricter glycemic management without significant hypoglycemia in spite of high-dose steroids and TPN in a challenging BMT population.

Despite studies showing improved outcomes, decreased length of stay, and cost savings with scheduled basal bolus insulin therapy [22], use of sliding scale insulin alone remains notoriously popular among providers, impeding standard of care. There are two major studies on Glucommander SQ version. The first was a retrospective, cross-over, observational study involving 993 non-critical patients across 9 hospitals in medical/surgical, cardiovascular, ER, and critical care units [23]. Authors investigated Glucommander versus provider managed SQ insulin dosing on percent of BG in target (140–180 mg/dL) and hypoglycemia events. Analysis was conducted before, during, and after Glucommander use. During Glucommander use, patients had significantly higher time in range (62 versus 47% and 36%; $P = 0.002$ and $P = 0.001$, before and after Glucommander) and less hypoglycemia readings < 70 mg/dL (1.9 versus 2.6% and 2.8%; $P = 0.001$ for both, before and after). A second subcutaneous (SQ) study described adoption of Glucommader at a 580-bed academic medical center [24•] with high prevalence of diabetes. Prior to introduction of Glucommander at this hospital, 95% of the time providers were using sliding scale insulin, with basal bolus insulin used 5% of the time. At month 1 and sustained through the 12-month study period, sliding scale use was reduced to 4% and basal bolus use improved to 96%. Hypoglycemia readings (< 70 mg/dL) was lower in Glucommander (1.74 versus 2.16%; $P < 0.001$) and severe hypoglycemia readings (< 40 mg/dL) were also reduced (0.11 versus 0.27%; $P < 0.0001$.) Percentage of BG in target (71–180 mg/dL) was higher in Glucommander (67.59 versus 60.97%; $P < 0.0001$) and rate of > 180 mg/dL was less in the Glucommander group (30.72 versus 36.88%; $P < 0.0001$). These studies demonstrate Glucommander SQ superiority in achieving greater percent time in range with fewer incidences of hypoglycemia by removing calculation errors and eliminating dose titration inertia. More importantly, SQ eGMS avoid excessive reliance on sliding scales by improving guidance on ordering basal/bolus insulin therapy.

EndoTool^{R}

In contrast with the other three commercial eGMS that use PID (proportional integral derivative) model with multiplier adjustments over time, EndoTool^{R} (Monarch Medical Technologies) uses MPC (model, predict, control) controller. Its sophisticated proprietary algorithms calculate insulin doses based on patient specific factors like type of diabetes, weight, kidney function, insulin on board (estimated residual extracellular insulin), and steroid use. Despite having both IV and SQ insulin algorithms, there are no studies to date on the SQ version.

Earliest studies on EndoTool investigated its impact on special surgical groups. Burn patients are a unique population that requires intensive glucose management to avoid infections and have higher propensity for hypoglycemia due to frequent interruptions in nutrition, multiple procedures, and malnutrition. A study including 18 burn ICU patients showed that time in a strict target range of 80–110 mg/dL was higher in EndoTool group compared to paper-based protocol (47 ± 17 versus 41 ± 16.6%; $P \leq 0.05$), with reduced hypoglycemia compared to historical rates [25]. A much larger study ($N = 1682$) of various critically ill surgical patients assessed EndoTool implementation on glycemic regulation, severe hypoglycemia rates, and hospital associated infections (HAI) [26]. In comparison of EndoTool use to traditional paper-based Portland protocol, rates of severe hypoglycemia readings (< 40 mg/dL) dropped from 1 to 0.05% ($P < 0.0001$) with hyperglycemia readings (BG > 150 mg/dL) also dropping by 50% ($P < 0.0001$). Authors could not attribute the

improvements in HgAIs to improved glycemic management with EndoTool due to confounding variables but noted that EndoTool significantly reduced the time spent by nurses on glucose management. A 2018 study by John et al., however, did not demonstrate similar results [27]. In evaluating impact of EndoTool on time on insulin drip, hypo- and hyperglycemia rates, authors saw a 3-h reduction in duration on the insulin infusion and a lower average rate of hypoglycemia events per patient compared to paper protocol (0.007 versus 0.036; $P = 0.17$); however, both groups were not statistically significant. Authors attributed lack of significance to conservative parameters set for EndoTool at the onset of rollout, implying that with longer use of the software and further training, more benefits could be reaped.

One of the longest trials looked back at the 7-year impact of EndoTool on glycemic management and national quality measures [28•]. Given that Center for Medicare and Medicaid Services (CMS) has deemed inadequate glucose management as a preventable condition with implications on financial reimbursements for hospitals, a system designed to make inpatient glucose management less taxing and error prone can impact downstream quality measures. This study at a community teaching hospital included 16,850 medical and surgical patients in ICU and intermediary/step-down units. With EndoTool, average time to target of < 180 mg/dL was 1.5–2.3 h with very low rates (0.4%) of glucose excursions once targets were achieved. Another notable finding was that year upon year, there was a drastic reduction in percent of glucose values < 70 mg/dL from 1.04 to 0.46% ($P < 0.0001$) by year 7. Moreover, over 7 years, only 0.03% of blood glucose readings were below 40 mg/dL. HAC-8 rates, which CMS has deemed as preventable and costly, also improved from 0.083 per 1000 patients in 2008 to 0.032 per 1000 patients in 2011, with the national average being 0.050 per 1000 patients in 2011. This is in line with results of an older study at a smaller institution comparing EndoTool implementation in 2009 to prior paper-based IV insulin infusion and two revisions to the paper-based protocol. Authors found that time in range was at 86% after EndoTool implementation versus 32–64% despite multiple revisions to existing paper protocol. Moreover, hypoglycemia < 70 mg/dL was 0.76% of BG readings with EndoTool, which was less than 2.4–5.4% in 60–79 mg/dL experienced by original and revised paper protocols [29].

Although prospective randomized controlled studies are lacking in the eGMS arena, there was one in evaluation of EndoTool's effectiveness compared to paper protocol [30]. A 2012 study at a Virginia based rural hospital randomized 300 cardiovascular surgery patients to either EndoTool IV protocol or Portland paper-based protocol. Although there were no differences in time to target, hypoglycemia, or mean glucose between the two groups, authors concluded that this was in part due to more patients in the paper protocol not receiving nutrition. Glucose variability was less with EndoTool (SD 18.3 versus 21.2 mg/dL; $P < 0.001$). The study also evaluated EndoTool's impact on nursing satisfaction and found that nurses were more satisfied with EndoTool than with the paper protocol (mean satisfaction score 8.4 out of 10 compared to 4.8 for paper; $P < 0.001$) and deviated less from EndoTool protocol (mean of 0.39 ± 1 versus 3 ± 4.3 times per patient; $P < 0.001$).

GlucoStabilizer™

GlucoStabilizer is a trademark of Indiana University Health that uses a linear multiplier to adjust the rate of intravenous insulin infusion. The ISF is increased or decreased based on an individual's response to treatment. It has both IV, SQ, and pediatric versions. Ample studies are published on the IV version and one study is dedicated to SQ version.

Two large multicenter trials were done on the GlucoStabilizer IV version in the ICU setting. The first study evaluated 2398 ICU patients over 2-year period following implementation of GlucoStabilizer [31]. Percentage of BG measurements at a stringent target < 110 mg/dL in the ICU in the 3 months before introduction of GlucoStabilizer program was 31.5% compared with 51.5% in the 3 months after introduction of the software ($P < 0.01$). This improvement was without increase in hypoglycemia (BG < 50 mg/dL at 0.4% of readings with GlucoStabilizer versus 0.5% prior to GlucoStabilizer). The same authors conducted a larger study without a control arm in 2009, following over 4000 ICU patients and targeting a tight blood glucose of 80–110 mg/dL using GlucoStablizer IV protocol [32]. Results showed 97% of patients achieving target range and remaining there 73% of the time for the 50-h duration of the insulin drip. Severe hypoglycemia (< 40 mg/dL) occurred in 4.25% of patients, but authors concluded that these were due to delays in rechecking BG when patient was hypogycemic; hypoglycemia incidence could have been lowered to 2% if timely BG monitoring were performed as instructed by the software. With prior meta-analysis demonstrating tight (< 110 mg/dL) glucose management in the ICU increasing risk of patients developing hypoglycemia compared to usual care (BG < 40 mg/dL 13.7 versus 2.5%; RR 5.13%; 95% CI, 4.09–6.43) [33], authors concluded that the use of eGMS is able to achieve the same intensive glucose management without the aforementioned high rates of hypoglycemia.

A smaller study from Tufts Medical Center compared a paper protocol to GlucoStabilizer IV in 197 critically ill surgical patients [34]. Importantly, patients were not excluded based on medical diagnosis or treatment with corticosteroids and/or enteral nutrition that predispose them to hyperglycemia. Results noted that despite higher BG in the GlucoStabilizer group at the start, they achieved lower mean BG compared to paper protocol (117 versus 135 mg/dL; $P = 0.0008$). Moreover, the eGMS group sustained greater time in

range defined as 95–135 mg/dL (68 versus 52%; $P = 0.0001$), and less percentage of time in BG < 70 mg/dL (0.51 versus 1.44%; $P = 0.04$) with less glycemic variability (+ 29 versus + 42; $P = 0.01$).

Use of Glucostabilizer has also been validated in special populations such as intrapartum women with diabetes [35]. American College of Endocrinology and American College of Obstetricians and Gynecologists recommend maintaining intrapartum maternal BG < 110 mg/dL as maternal hyperglycemia preceding delivery is predictive of neonatal hypoglycemia [36]. This study concluded that GlucoStabilizer was superior in achieving target glucose values (70–100 mg/dL) at delivery (81.8 versus 9.1%; $P < 0.001$) with a lower mean glucose (102.9 versus 121.7 mg/dL; $P = 0.02$) and non-statistical reduction in maternal hypoglycemia compared to standard protocol. Using eGMS in the obstetrics settings is a novel concept that has not been previously studied. The ability of eGMS to adjust the ISF during labor when stress and insulin resistance are dynamic variables makes eGMS ideal for this situation. In contrast, the Intensive versus Standard Treatment of Hyperglycemia and Functional Outcomes in Patients with Acute Ischemic Stroke (SHINE) randomized controlled trial evaluated post-ischemic stroke outcomes between intensive BG management (80–130 mg/dL) using GlucoStabilizer IV to conservative BG management (80–179 mg/dL) using SQ insulin sliding scale administered every 6 h. Unsurprisingly, it showed worse rates of severe hypoglycemia (< 40 mg/dL) in patients in the infusion group compared to sliding scale group (2.6 versus 0%; risk difference 2.58%, 95% CI 1.29 to 1.41%) with higher BG in the SQ group [37]. However, a study designed to compare SQ sliding scale to an infusion is susceptible to number of confounders.

The single available GlucoStabilizer SQ (GS-SQ) study was published in 2008 without a control arm [38]. Authors noted that institutions involved had problems with the prior SQ insulin order set due to providers incorrectly ordering correction scale orders only and inconsistent nursing administration of basal/bolus insulin therapy. Results were impressive. With over 1700 treated patients on GS-SQ protocol, 40.5% of BG were in range of 100–150 mg/dL, and 69.8% were in wider range of 70–180 mg/dL. Percent of hypoglycemia < 40 mg/dL was low at 0.18% of readings. GS-SQ also has built-in warnings for potentially unsafe insulin doses and alerts nurses to call the physician/NP/PA for hyperglycemia when BG > 350 mg/dL or two consecutive BGs > 220 mg/dL.

GlucoCare™

Based on the Yale infusion protocol, Pronia Medical LLC developed its computerized insulin protocol, GlucoCare, in 2007 and obtained FDA clearance for the 100–140 mg/dL target range, with subsequent target range modifications. GlucoCare is limited to IV and transition protocols. Original data on the non-computerized Yale intense infusion protocol targeting BG of 100–139 mg/dL showed that the median time to reach target was 9 h with 66% in the narrow target of 80–139 mg/dL and 93% in the broad target of 80–199 mg/dL, with only 0.3% of BG total readings < 60 mg/dL [39]. The protocol was widely accepted by ICU nurses due to its ease of use. After computerization and commercialization of Yale insulin infusion protocol as GlucoCare, PID controller and linear equation with a multiplier are used for rate calculation, requiring only manual entering of the glucose value.

Two studies were published since the computerization of the Yale Protocol into GlucoCare software. The first was a retrospective analysis of all patients admitted to the ICU at multiple institutions undergoing intravenous insulin infusion using GlucoCare targeting BG of 100–140 mg/dL. The authors specifically evaluated hypoglycemia incidences and found that of 55,162 BG readings of 1657 patients, only 0.01% of readings showed severe hypoglycemia (< 40 mg/dL). Moderate hypoglycemia (BG 40–69 mg/dL) occurred in 1.13% of BG readings, and of those, 15.3% were attributed to staff nonadherence to protocol such as not giving dextrose as recommended by the program or not checking BG early when BG was rapidly falling [40]. A second study looked at refinements of the Yale protocol and their impact on reducing hypoglycemia further. There were revisions of target BG within the GlucoCare system from 100–140 to 120–140 mg/dL (GlucoCare 120–140) and single target of 140 mg/dL (GlucoCare 140). The final modification to the system was called GlucoCare 140(B), and included the addition of bolus insulin "mid-protocol" during insulin infusion to reduce peak insulin rates for insulin-resistant patients [41]. Mean BG achieved by each protocol (100–140, 120–140, 140, and 140B) were 133.4 mg/dL, 136.4 mg/dL, 143.8 mg/dL, and 146.4 mg/dL, respectively, with decrease in hypoglycemic BG readings < 70 mg/dL when moved from standard 100–140 mg/dL Yale protocol to modified protocols ($P < 0.001$). Raising lower BG target from 100 to 120 mg/dL (GlucoCare 120–140) led to amelioration of hypoglycemic BG readings (< 70 mg/dL) from 0.998 to 0.367%. Raising the target to single 140 mg/dL (GlucoCare 140) further diminished hypoglycemic BG readings (< 70 mg/dL) to 0.256%; adding boluses in protocol 140B led to further reduction to 0.04%. GlucoCare 140B protocol also eliminated BG < 60 mg/dL while achieving mean BG of 140–150 mg/dL. The modifications are in line with ADA/AACE guidelines (140–180 mg/dL) as well as Society of Critical Care Medicine guidelines recommending ≤ 150 mg/dL in critically ill [42].

GlucoCare, unlike other eGMS, have compared various target ranges and single digit targets for BG management within its software. These show great promise of achieving tighter BG outcomes while dramatically improving rates of hypoglycemia.

Institutional eGMS

Home-grown computerized insulin drip calculators are also options for reducing hypoglycemia rates while improving glycemic management. Unlike commercial eGMS, these can be integrated within the hospital electronic health record without the need for third party software, therefore reducing implementation costs for the institution. At our institution, our insulin infusion algorithm utilizes an insulin sensitivity coefficient and both the blood glucose value and rate of change to determine the insulin infusion rate. Initial studies have shown that across multiple units with over 6000 patients and 270,000 readings, our insulin infusion computer calculator was able to achieve a BG target of 90–180 mg/dL 83% of the time with only 0.01% of readings with severe hypoglycemia < 40 mg/dL and very high nursing satisfaction [43]. Thus, home-grown computerized insulin protocols can offer safe and efficacious options for institutions.

Obstacles to eGMS Use

Despite numerous advantages of the eGMS, there are also disadvantages that need to be discussed. One of the major downsides of eGMS is cost. They are expensive to implement and incur hefty costs to maintain these systems. Out of all the commercial eGMS, GlucoCare™ is advertised as the most cost-effective.

Another barrier to eGMS is their integration with hospital networks and EHR. Although they advertise simplicity, the initial integration and subsequent maintenance still require extensive information technology support. Security of these systems' cloud-based integration of patient data needs to be thoroughly vetted to prevent malware attacks encroaching on patient privacy. Moreover, like any system-wide change, aggressive education and training of staff are needed prior to implementation to ensure success and institution-wide acceptance. Implementation is likely to succeed when done in a phased approach, on single units, or in individual hospitals in a multi-hospital network [44]. Initiation of a new eGMS also requires oversight, collaboration, and buy-in from the institution's glycemic management committee, pharmacy, nursing, laboratory, and patient safety committee.

As with any electronic system, there are inherent workflow issues to consider including downtime options in case of power failures or during EHR downtime, and how simple these downtime processes are for staff to follow. Although eGMS improve timely fingerstick glucose checks by alerting nurses, alert fatigue poses realistic challenges. Automation of insulin delivery also does not facilitate timely meal tray delivery. Each institution must still tackle these challenges with respective multidisciplinary teams, including nutrition services, nursing, pharmacy, endocrinology, and ordering providers [45].

Automated insulin delivery systems are excellent resources for institutions that lack interdisciplinary diabetes management teams, but they are not substitutes for experience and knowledge. One drawback to commercial eGMS is the lack of human component available to evaluate outpatient regimens based on individualistic variables. Although the algorithms can use current glucose trends to predict outpatient regimen, this does not translate into successful outpatient control. A diabetes management team can recommend individualized outpatient therapy based on patient-specific factors such as self-care behaviors, e.g., medications and diet, comorbidities or intolerances, and finances to help prescribe other oral or injectable medications for individualized outpatient transitions. Automated insulin delivery systems are unable to consider the human aspects of these multifaceted components of diabetes care.

Conclusion

Insulin is a high-risk medication and the availability of eGMS may serve to mitigate medication errors and improve patient safety.

Inpatient glycemic management is complex and fluid, affected by multiple variables, all requiring attention to details. Not all institutions have diabetes management teams or on-site endocrinologists, specially nurse practitioners or physician assistants to fine tune these parameters. Therefore, eGMS may provide an attractive alternative for successful glucose management. All four eGMS target hyperglycemia, hypoglycemia, and glycemic variability.

Although debate still exists on the optimum inpatient blood glucose targets, use of automated insulin delivery systems discussed here can achieve targeted glucose ranges while mitigating risk of hypoglycemia.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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