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LETTER TO THE EDITOR

Algorithm Maxima for Intravenous Insulin Infusion

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Dear Editor,

In a case series of 378 patients, we attempt to identify a threshold rate of continuous intravenous insulin infusion associated with increased risk of hypoglycemia. Much of the relevant medical literature focuses upon glycemic targets, often discussed in relation to specific populations.[1] We anticipate a future day when glycemic targets routinely may be personalized according to preadmission glycemia.[2–4] At the time of the planning of our study, a consensus goal for blood glucose (BG) during intravenous insulin infusion was 100–150 mg/dL, a hypoglycemia alert value was defined as BG ≤70 mg/dL, and clinically significant hypoglycemia as BG <54 mg/dL.[5,6] It was hypothesized that a threshold value of peak insulin infusion rate might be discerned, above which the occurrence of BG <54 mg/dL became excessive.

In a retrospective observational study of eligible consecutive intravenous insulin infusion treatment courses, we aimed to determine odds ratio (OR) and relative risk (RR) for BG <54 or ≥54 mg/dL according to peak insulin infusion rate. The Saint Joseph Hospital Institutional Review Board reviewed and approved the study.

Three institutional column-based tabular algorithms for intravenous insulin infusion were identified as the ''study algorithms,'' each having the same goal range 130–149 mg/dL and acceptable range 100–149 mg/dL for BG control, recommending titration every 1–2 h, similar in design and sharing some columns, but differing with respect to aggressiveness of initiation and titration rules.[7] The maximum insulin infusion rate in the highest column under the ''Conservative'' and ''Standard Default'' algorithms is 14.6 units/h and under the ''Aggressive'' algorithm is 29.2 unit/h.

The unit of observation was the earliest qualified treatment course of a unique patient using insulin infusion rate values represented under at least one of three ''study algorithms.'' Data were collected from the electronic medical record EPIC® for consecutive treatment courses ordered within the timeframe between July 1, 2012 through August 31, 2016 at Saint Joseph Hospital in the Chicago Lakeview neighborhood, an urban academic hospital having a combined medical and surgical intensive care unit (ICU). Inclusion required orders for continuous intravenous regular insulin infusion under one of the three ''study algorithms.'' Exclusion criteria consisted of age under 18, pregnancy, hyperglycemic crisis, treatment for hypertriglyceridemia, and occurrence of hypoglycemia before peak insulin infusion rate without any hypoglycemia after peak insulin infusion rate during the data collection interval.

After identification of 611 potential cases having orders for intravenous regular insulin infusion, 233 were disqualified having one or more of the following criteria: no record of insulin administration by intravenous infusion (40), treatment with intravenous insulin infusion conducted for <4 h (26), pregnancy (77), inability to identify a ''study algorithm start time'' (8), recurring use of insulin infusion rates not represented on at least 1 of the 3 ''study algorithms'' (3), ''Hyperglycemic Crisis'' algorithm ordered with use confirmed by review of insulin infusion rates (48), hyperglycemic crisis diagnosis confirmed by chart review of clinical data (75), treatment for hypertriglyceridemia (12), contradiction between nonzero insulin infusion rates under 2 otherwise qualified orders (6), qualified treatment course that was contradicted by the Full Administration Report of a disqualified earlier

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treatment course (1), and BG ≤70 mg/dL but none occurring subsequent to peak insulin infusion rate (5). Inability to recognize insulin infusion rate assignments characteristic of any institutional ''study algorithm'' resulted in exclusion, but it was not consistently possible or required to specify which algorithm was being followed.

We collected data at timepoints inclusive of initiation through 12 h after termination of insulin infusion under the study algorithm or the time of patient discharge, whichever was earlier. For each value of peak insulin infusion rate, the numbers of cases having or not having peak insulin infusion rate ≥ candidate value, and having or not having BG <54 mg/dL subsequent to peak insulin infusion rate, were used to compute ORs and RR with 95% confidence interval (95% CI) for BG <54 mg/dL.

Excel® was used for data storage and preliminary analyses (Microsoft Office 2016). Further analysis of de-identified data was performed using Social Science Statistics (https://www.socscistatistics.com/) and Vassarstats website for Statistical Computation (http://vassarstats.net/anova1u.htm, http://vassarstats.net/odds2x2.html), accessed in 2019 and 2020. Statistical methods are shown as footnotes to online Supplemental Table 1. Significance was assigned at *P*-values <0.05.

The sample consisted of the first eligible treatment course of each of 378 unique patients (Fig. 1). When 353 patients having no BG <54 mg/dL were compared with 25 having at least one BG <54 mg subsequent to peak insulin infusion rate, there were no statistical differences between groups for the potential predictors of age, HbA1C, admission creatinine above reference range, sepsis by face-sheet coding, postoperative status, vasopressor use, corticosteroid use, additional antihyperglycemic therapy, or duration of observation during study algorithm treatment, and in-hospital mortality did not differ significantly, $n = 42$ (11.9%) versus $n = 6$ (24.0%).

The peak insulin infusion rate having greatest OR and RR for BG <54 mg/dL was 12.2 units/h. For patients having or not having BG <54 mg/dL, occurring subsequent to peak IR ≥12.2 or <12.2 units/h, there were OR 2.74 ($P = 0.03$) and RR 2.52 (1.18, 5.40). Some of the associated factors differed according to peak insulin infusion rate, as shown in the online Supplemental Table 1.

The objective of this study was to ask whether a threshold for high-dose insulin delivery during intravenous insulin infusion could be identified as a risk factor for hypoglycemia. Among treatment courses having peak insulin infusion rate <12.2 units/h, the occurrence of BG <54 mg/dL subsequent to

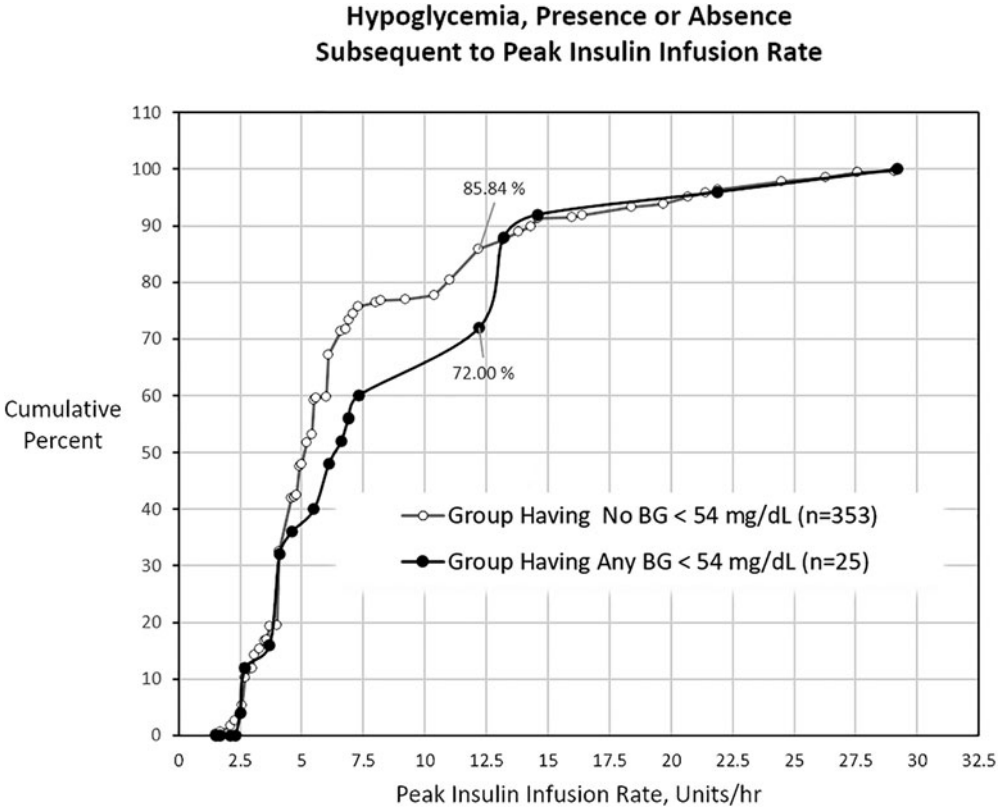

FIG. 1. Patients having or not having an episode of BG <54 mg/dL subsequent to peak insulin infusion rate; group size according to peak insulin infusion rate. Insulin infusion rate and BG data were collected at timepoints from study algorithm initiation until 12 h after termination of insulin infusion or the time of patient discharge, whichever was earlier. Among those with any event of BG <54 mg/dL subsequent to peak insulin infusion rate ($n = 25$), the numbers of patients were 15, 3, and 7 having peak insulin infusion rate, respectively, <12.2, 12.2, and >12.2 units/h. For treatment courses having peak insulin infusion rate at or below each value shown as independent variable, the cumulative percentage of the group having no event of BG <54 mg/dL subsequent to peak insulin infusion rate ($n = 353$) is compared to the percent of the group having any BG <54 mg/dL subsequent to the peak insulin infusion rate ($n = 25$). BG, blood glucose.

peak insulin infusion rate was 5.0% of patients, $n = 15/299$. In comparison, among the patients having peak insulin infusion rate ≥12.2 units/h, the occurrence of BG <54 mg/dL was 12.7% of patients, $n = 10/79$ ($P = 0.03$). Postoperative status and some related associated factors were greater in the group having peak insulin infusion rate ≥12.2 units/h. Although mean BG control met consensus goals, there were higher values for times to target and slightly higher means of BG after first attaining target in the group receiving peak insulin infusion rate ≥12.2 units/h, suggesting greater insulin resistance, probably mostly associated with medication use and surgical stress. In-hospital mortality did not differ.

In the present series, 79/378 or 20.9% of patients experienced any BG ≤70 mg/dL. At another hospital in our health care system, when treated under our ''Standard Default'' column-based algorithm having design similar to that of our ''Aggressive'' algorithm but with lower algorithm maximum insulin infusion rate, for comparison 5/53 or 9.4% of patients experienced BG <70 mg/dL and none experienced BG <54 mg/dL.[7]

In the general management of medical or postoperative patients, algorithm design must provide monitoring and titration rules that respond to the variability of insulin sensitivity during early care in the ICU, short-term use of pressors and corticosteroids, and the risk of abrupt or unforeseen interruption of carbohydrate exposure.[8] Adherence to algorithm rules is burdensome to staff, such that timely downtitration sometimes fails to occur. Mid-protocol bolus therapy may offer greater safety than progressive upward titration of the hourly infusion rate.[9] The benefits of computerization of well-designed algorithms have been demonstrated.

Some safe and highly effective algorithms specify conservative maxima for continuous insulin infusion.[10] Experimentally, during intravenous insulin infusion at least 2 h may be required at each infusion rate to reach steady state.[11] A saturable dose–response relationship may be evident, limiting the effectiveness of progressively greater delivery of insulin.[10,12,13] In sharp contrast to some present-day algorithms, early description of the successful Sprint protocol refers to a protocol maximum rate of continuous intravenous insulin infusion of 6 units/h.[13] In a clinical setting, during aggressive upward dose titration the retention of ineffective insulin at interstitial sites may create risk for subsequent hypoglycemia. During temporary insulin resistance, most patients having normal renal function may tolerate high infusion rates. However, recurrent or delayed episodes of hypoglycemia occur in a small number of patients.[7,14,15] Therefore, among temporarily insulin-resistant patients, a preventive measure may be to limit the delivery of ineffective insulin.

We did not seek to evaluate, endorse, or reject specific glycemic targets. Generalizability is limited by algorithm design and lack of complete information about the population studied. Without matching of cases or randomization, it cannot be ascertained whether lower infusion rates would have jeopardized time-to-target, maintenance of target range control after achieving target, control of glycemic variability, or any hard outcomes. A full analysis of insulin delivery necessitates integration of insulin effect from insulin infusion rates delivered over multiple intervals in past time, including potentially home, intraoperative, or emergency room delivery.

Definition of high-dose insulin delivery and identification of population-appropriate algorithm maxima may be relevant for both computerized systems and also for sites lacking computerization. Provider override and advance provision for exceptional requirements should remain options under any set of algorithm rules.[16] In this report of a noncomputerized system, exploratory findings in our population suggest that an excess of hypoglycemia may be associated with use of peak insulin infusion rate ≥12.2 units/h.

Supplementary Material

Supplemental Table 1

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