



## ORIGINAL ARTICLE

## Effect of Overlapping Insulin Glargine Administration in Decreasing Incidence of Hyperglycemia after Discontinuation of Intravenous Insulin Infusion

Jillian B Searle, PharmD\*, Veronika Latawiec, PharmD, Micaela Carroll Powner, PharmD, BCPS, Andrea Winston, PharmD, BCACP and Dorothy Wakefield, M.S., PStat

Saint Francis Hospital & Medical Center, Trinity Health of New England, CT, USA



\*Corresponding author: Jillian B Searle, PharmD, Saint Francis Hospital & Medical Center, Trinity Health of New England, 114 Woodland Street, Hartford, CT 06105, USA, Tel: (860)-714-4491, Fax: (860)-714-8000

### Abstract

**Background:** The study purpose was to assess the incidence of hyperglycemia in patients being transitioned from an IV infusion to subcutaneous (SC) insulin. Study staff evaluated whether overlapping SC with IV insulin decreased the incidence of hyperglycemia.

**Methods:** This study is an Institutional Review Board-approved retrospective chart review. Patients were included if they were between the ages of 18 and 89, admitted between 3/1/20 and 12/31/21, received an IV insulin infusion for at least 24 hours, and were previously diagnosed with type I or II diabetes. Patients who did not receive insulin glargine and those diagnosed with diabetic ketoacidosis or hyperosmolar hyperglycemia syndrome on admission were excluded. Electronic medical record reports were built to identify patients that received an IV insulin infusion and SC insulin glargine. Patients meeting eligibility criteria were included in the analysis. Outcomes for patients receiving SC insulin and IV infusion overlap were compared to those who transitioned without overlap. Based on the hypothesis that there would be a difference of 30% in the incidence of hyperglycemia between groups, 36 patients per group were required to achieve 85% power. Chi-squared, t-test, and Wilcoxon rank-sum tests were used to detect differences between groups with statistical significance determined using  $p \leq 0.05$ . The primary outcome was the incidence of hyperglycemia (blood glucose (BG)  $\geq 180$  mg/dL) and secondary outcomes were the incidence of hypoglycemia (BG  $\leq 70$  mg/dL), correction of hypoglycemia using dextrose, adjustments made to the insulin glargine dose, and the need to restart the IV insulin infusion during the admission.

**Results:** There was no significant difference in the incidence of hyperglycemia between groups. There was also no significant difference in the incidence of hypoglycemia or other secondary outcomes. Specific results from data analysis will be presented.

**Conclusion:** Glycemic control in diabetes patients is crucial due to the significant potential for negative outcomes surrounding uncontrolled blood glucose. No difference was detected between groups for all endpoints in this study. The results of this study were aimed at outlining the need for a protocol establishing the appropriate transition from IV insulin infusion to SC insulin. Based on these results, there was no preferred method for transitioning IV to SC insulin in hospitalized patients.

### Keywords

Hyperglycemia, Transition, Overlap, Glycemic control, Insulin glargine, Insulin drip

### Abbreviations

BG: Blood glucose; IV: Intravenous; SC: Subcutaneous

### Introduction

Glycemic control in patients with diabetes is crucial due to the significant potential for negative outcomes surrounding uncontrolled blood glucose (BG). Both hyper- and hypoglycemia among hospitalized patients are associated with an increased risk for complications, prolonged length of stay, an exorbitant medical cost burden, and worsened mortality [1]. The American Diabetes Association (ADA) currently recommends a

target glucose between 140 and 180 mg/dL for critically ill patients in the ICU in addition to patients admitted to general medicine and surgery settings. The Society of Critical Care Medicine (SCCM) published The Guidelines for Use of an Insulin Infusion for the Management of Hyperglycemia in Critically Ill Patients, recommending the initiation of insulin therapy with a BG  $\geq$  150 with a goal BG of 100-150 mg/dL using a protocol that minimizes hypoglycemia [2].

Diabetes is a prevalent health condition around the world, and specifically in the United States, carrying an estimated total impact of approximately 37.3 million Americans, or 11.3% of the total US population [3]. The economic burden of diagnosed diabetes on the United States' healthcare system is \$237 billion in total, with \$237 billion being incurred in direct medical costs and \$90 billion in reduced productivity [4]. Major contributors to these medical costs are heightened infection rates, longer hospital, and intensive care stays, and increased mortality. Substantial observational evidence has supported an association between hyperglycemia and poor outcomes, while other trials have failed to show a mortality benefit with intensive glycemic control. As a result, the means for achieving glycemic targets in hospitalized patients has provided confusion and a lack of guideline-directed standardization on the topic.

Critically ill patients experiencing hyperglycemia who are admitted to higher acuity hospital care units are recommended to be treated first-line with an intravenous insulin infusion. However, numerous guideline recommendations suggest transitioning to subcutaneous insulin once patients are eating regular meals or are transitioned to lower acuity care units [5,6]. The ADA and American Association of Clinical Endocrinologists (AACE) recommend that scheduled SC insulin is preferred for maintaining glucose control in non-ICU level-of-care patients with hyperglycemia, whether due to diabetes or stress hyperglycemia. Due to the significant potential for negative outcomes surrounding uncontrolled blood glucose, there is a significant amount of guidance surrounding glycemic control in critically ill adults and initiating these patients on an intravenous insulin infusion but there is a gap in knowledge in the literature for strategies on transitioning from intravenous (IV) to subcutaneous (SC) insulin.

The purpose of this study was to assess the incidence of hyperglycemia in patients being transitioned from an IV insulin infusion to SC insulin glargine. This study evaluated whether overlapping SC insulin with a continuous IV insulin infusion before transitioning from IV to SC insulin decreased the incidence of hyperglycemia. The primary outcome was the occurrence of hyperglycemia (BG  $\geq$  180 mg/dL) in the 24-hour period after the continuous insulin infusion was stopped. Secondary outcomes investigated the

occurrence of hypoglycemia (BG  $\leq$  70 mg/dL) in the 24-hour period after transitioning from IV to SC insulin, the correction of hypoglycemia using dextrose, adjustments made to the insulin glargine dose, and the need to restart the continuous insulin infusion during the hospital admission.

Many hospitals have implemented protocols that assess the appropriate amount of insulin that should be administered with titration and time-specific instructions. The results of this study were aimed towards outlining the need for a protocol establishing the appropriate transition from IV insulin infusion to SC insulin.

## Methods

This study is an Institutional Review Board-approved, single-center, retrospective chart review of patients in a 617-bed teaching inpatient hospital that is part of a larger national health system. Patients were included if they were between the ages of 18 and 89, were admitted to the hospital between March 1<sup>st</sup>, 2020, and December 31<sup>st</sup>, 2021, received a continuous insulin infusion for at least 24 hours and were previously diagnosed with type I or II diabetes mellitus. Patients who did not receive insulin glargine or who were diagnosed with diabetic ketoacidosis or hyperosmolar hyperglycemia syndrome were excluded.

Electronic Medical Record (EMR) reports were built to generate lists of patients that received a continuous IV insulin infusion and insulin glargine. Patients identified through these reports were evaluated for eligibility criteria and compared to determine which patients received SC overlap before the continuous infusion was discontinued. Based on the hypothesis that there would be a difference of 30% in the incidences of hyperglycemia between both groups, 36 patients were required in each group to achieve 85% power. Differences between groups were determined using  $p \leq 0.05$  and detected using Chi-squared, t-test, and Wilcoxon rank-sum tests.

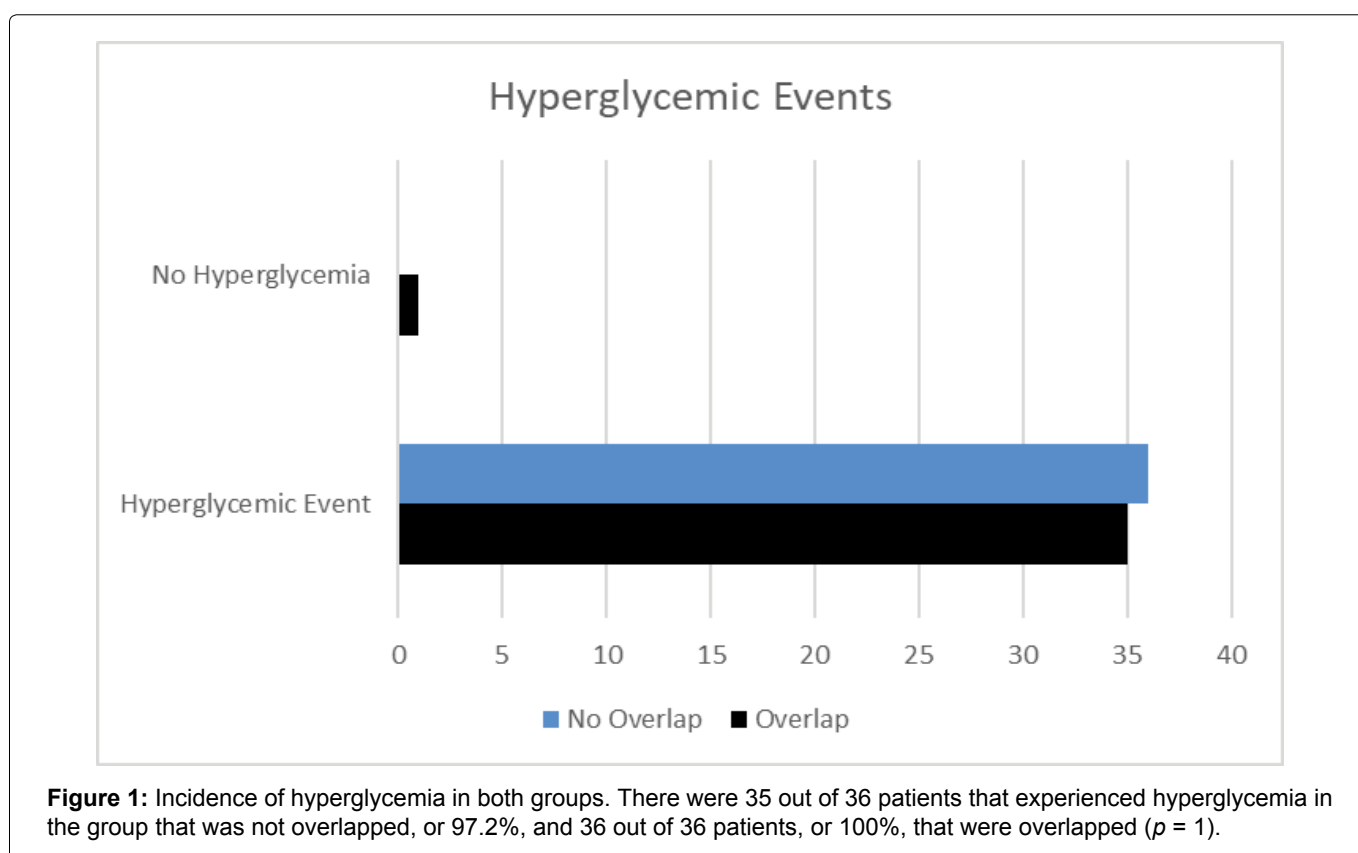
EMR reports were utilized to identify patients receiving IV insulin and SC insulin, and subsequently were compared to identify patients who received both. Patients were then randomly evaluated further for inclusion and exclusion criteria by EMR chart search, medication administration records, laboratory values, diagnoses, patient demographics, and continuous infusion records. The first 36 patients per group, overlapped and not overlapped patients, created two cohorts and were included in data analysis. Coded data was then collected in relation to primary and secondary outcomes.

## Results

Baseline characteristics were similar between groups (Table 1). Steroid administration was numerically more common in the group that received IV and SC overlap,

**Table 1:** Baseline characteristics.

|   | Group #1: No Overlap | Group #2: Overlap | P-value |
|---|----------------------|-------------------|---------|
| Age in years, median (SD)                         | 64 (12, SD)          | 66 (12, SD)       | 0.49    |
| Sex   |                      |                   |         |
| Female, n(%)                                      | 15 (41.7%)           | 14 (38.9%)        | 0.81    |
| Male, n(%)  | 21 (58.3%)           | 22 (61.1%)        |         |
| Diabetes Diagnosis                                |                      |                   |         |
| Type 1  | 0 (0%)               | 1 (2.8%)          | 0.37    |
| Type 1.5  | 1 (2.8%)             | 0 (0%)            |         |
| Type 2  | 35 (97.2%)           | 35 (97.2%)        |         |
| A1c on Admission                                  | 8.88 (1.7, SD)       | 8.89 (2, SD)      | 0.99    |
| Steroid Administration                            | 11 (30.6%)           | 19 (52.8%)        | 0.056   |
| Duration of IV Insulin Infusion, mean hours       | 37                   | 36                | 0.83    |
| Dose of SC insulin administered day 0, mean units | 30.7                 | 42.3              | 0.021   |



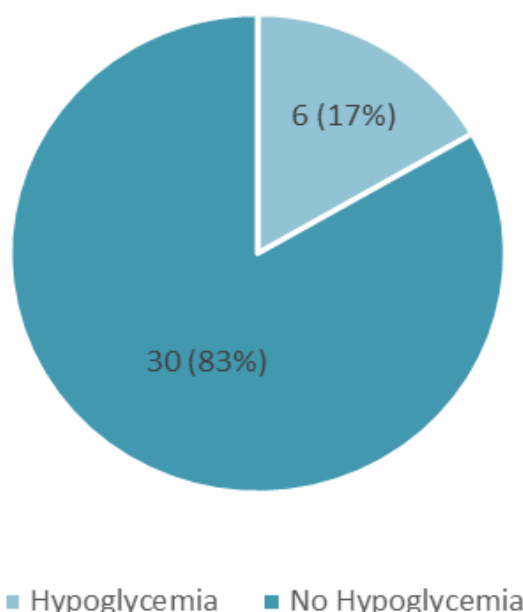
but this difference was not significantly different ( $p = 0.056$ ). The majority of patients, 35 in each group (97.2%), were diagnosed with type 2 diabetes. The dose of SC insulin, in units, administered on day 1, or the 24 hours after transitioning from SC to IV insulin, was higher in the overlap group ( $p = 0.021$ ), with a mean [IQR] dose of 30.7 units [20, 62], versus 42.3 units [19, 38] in the group that did not receive overlap.

Thirty-six patients were overlapped with SC insulin glargine upon transitioning from a continuous IV insulin infusion to SC insulin glargine. Overlap times ranged from 0.5 hours to 23 hours, with a median [IQR] overlap time of 3 hours [1.5, 8.5]. In the overlap group, the patients received anywhere from 8 to 120 units of glargine on day 0, or the 24 hours prior to discontinuation of the

IV infusion, with a median [IQR] of 30 units [20, 40]. Patients who transitioned directly from IV to SC insulin without overlap started SC therapy a median [IQR] of 6 hours [2, 22] after stopping the IV infusion.

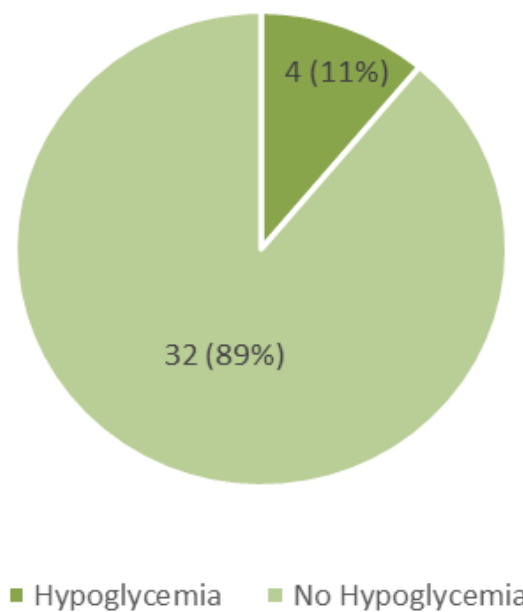
No difference was found between groups for the primary outcome, or the incidence of hyperglycemia. The primary outcome occurred in 35 out of 36 patients who were not overlapped (97.2%), and 36 out of 36 patients (100%) that were overlapped ( $p = 1$ ) (Figure 1). The incidence of hypoglycemia was also found to be equal between groups, with an event rate of 6 out of 36 patients (16.7%) in the not overlapped group, and 4 out of 36 patients (11.1%) in the overlapped group ( $p = 0.496$ ) (Figure 2). The average lowest recorded blood glucose readings were similar between groups.

### Group 1: No Overlap



**Figure 2:** Incidence of hypoglycemia among the group that was not overlapped SC and IV insulin doses. 83.3% of patients in the group that was not overlapped experienced a hypoglycemic event, and 16.7% of these patients did not experience hypoglycemia.

### Group 2: Overlap



**Figure 3:** Incidence of hypoglycemia among the overlap group. 88.9% of patients in the overlap group did not experience hypoglycemia, whereas 11.1% of patients in this group experienced hypoglycemia.

The average highest recorded blood glucose readings were numerically higher in the overlapped group ( $p = 0.074$ ). The median highest blood glucose in the overlap group was 371 [320, 473], and 374 [285, 412] in the not overlapped group. Blood glucose readings on administration were similar between groups ( $p = 0.951$ ) (Figure 3).

The adjustment in the SC insulin glargine dose was higher in the overlapped group than the not overlapped group ( $p = 0.031$ ). An average increase of 41 units and 32 units of SC insulin glargine, respectively, was required to address high blood glucose readings in patients after transitioning from IV to SC insulin.

No differences were found between groups regarding the total duration of time patients were treated with the IV insulin infusion ( $p = 0.827$ ), nor the need to restart the IV insulin infusion during the hospitalization ( $p = 0.306$ ). The average duration of time patients were treated with the IV insulin infusion was 37.1 hours in the not overlapped group and 35.9 hours in the overlapped group. Data for this parameter was highly skewed, so a Wilcoxon rank-sum test was used to establish significance.

## Discussion

Glycemic control in diabetes is crucial as hyper- and hypoglycemia among hospitalized patients are associated with an increased risk for complications,

length of stay, cost burden, and mortality. The results of this study were aimed towards outlining the need for a protocol establishing the appropriate transition from intravenous to subcutaneous insulin to reduce the incidences of hyper- or hypoglycemia in hospitalized patients. Previously published literature had suggested a between-groups difference in the incidence of hyperglycemia of 30%, therefore establishing 36 patients per group to achieve 80% power. In this study, no difference was detected upon transitioning IV to SC insulin in these patients.

The patients who received steroids were numerically more likely to be overlapped, seeming to be a strategic and clinical decision on the part of the medical teams. Providers and pharmacists likely postulated that patients on steroids would have a more resistant or significant hyperglycemia, prompting them to initiate SC insulin prior to the discontinuation of the IV insulin infusion.

The overlap group required a higher mean dose of SC insulin glargine (41 units) than the not overlapped group (32 units) in the 24 hours post-transition from IV to SC insulin. This was a paradoxical finding as it was expected that the group receiving 24 hours of IV and SC overlap would require less insulin due to the concomitant IV infusion. Additionally, the average highest blood glucose reading was numerically higher in the overlap group (441 mg/dL) versus the non-overlapped group (349 mg/dL). Since the highest blood glucose maximum in the

overlap group of 1643 mg/dL was an exponentially high value and an outlier, it increased the mean.

Several limitations were present which could confound the findings of this study. Results were limited by the high incidence of hyperglycemia in both groups. Although both the ADA and AACE establish recommendations for a target blood glucose of 140-180 mg/dL in hospitalized patients, there are instances in which a tighter or a looser blood glucose goal may be indicated. With the high acuity patients included in this study, higher target blood glucose levels may have been more realistic. Even a single BG above 180 mg/dL constituted hyperglycemia per our definition, but the clinical relevance of this was less clear. Rather than collecting a single high point-in-time glucose and reporting it as hyperglycemia, utilizing repeated high glucose readings or an average may have been advantageous, as blood glucose can fluctuate rapidly throughout the day.

Study design may have further confounded these findings, as both the parameters for overlap time, or the time from first SC administration until IV discontinuation, and the gap time, or the time from IV discontinuation until the first SC administration, were not outlined or limited in any way. The small sample size also disallowed for a post-hoc analysis assessing whether higher gap times were associated with hyperglycemia or whether smaller overlap times were commonly found to be associated with hypoglycemia. Lastly, the patients' nutritional status, whether they were on a 2000 calorie

diet or whether they were NPO was not considered upon evaluating the incidences of our primary and secondary outcomes, hyper- and hypoglycemia. A larger prospective randomized study in the future would likely be more revealing with further insight regarding how to manage patients being transitioned from an IV insulin infusion to SC insulin.

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