EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2022;37:444-454
https://doi.org/10.3803/EnM.2021.1341
pISSN 2093-596X · eISSN 2093-5978

Effect of the Concomitant Use of Subcutaneous Basal Insulin and Intravenous Insulin Infusion in the Treatment of Severe Hyperglycemic Patients

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Background: No consensus exists regarding the early use of subcutaneous (SC) basal insulin facilitating the transition from continuous intravenous insulin infusion (CIII) to multiple SC insulin injections in patients with severe hyperglycemia other than diabetic ketoacidosis. This study evaluated the effect of early co-administration of SC basal insulin with CIII on glucose control in patients with severe hyperglycemia.

Methods: Patients who received CIII for the management of severe hyperglycemia were divided into two groups: the early basal insulin group ($n=86$) if they received the first SC basal insulin 0.25 U/kg body weight within 24 hours of CIII initiation and ≥4 hours before discontinuation, and the delayed basal insulin group ($n=79$) if they were not classified as the early basal insulin group. Rebound hyperglycemia was defined as blood glucose level of >250 mg/dL in 24 hours following CIII discontinuation. Propensity score matching (PSM) methods were additionally employed for adjusting the confounding factors ($n=108$).

Results: The rebound hyperglycemia incidence was significantly lower in the early basal insulin group than in the delayed basal insulin group (54.7% vs. 86.1%), despite using PSM methods (51.9%, 85.2%). The length of hospital stay was shorter in the early basal insulin group than in the delayed basal insulin group (8.5 days vs. 9.6 days, $P=0.027$). The hypoglycemia incidence did not differ between the groups.

Conclusion: Early co-administration of basal insulin with CIII prevents rebound hyperglycemia and shorten hospital stay without increasing the hypoglycemic events in patients with severe hyperglycemia.

Keywords: Insulin, long-acting; Hyperglycemia; Diabetes complications; Diabetic ketoacidosis

INTRODUCTION

Intravenous (IV) insulin infusion is an effective method to achieve and maintain glycemic control in patients with diabetes mellitus (DM) in critical care settings [1]. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are serious acute metabolic complications of DM, which are known as hyperglycemic crises. The mainstay in the treatment of DKA and HHS involves the administration of IV insulin infusion [2]. Most treatment algorithms recommend the administration of an

Received: 25 November 2021, **Revised:** 18 April 2022, **Accepted:** 2 May 2022

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IV insulin bolus, followed by continuous intravenous insulin infusion (CIII) [3]. CIII is an essential step for restoring cellular metabolism, reducing hepatic gluconeogenesis, and suppressing lipolysis and ketogenesis [4]. CIII should be administered based on validated protocols that permit predefined adjustments in the infusion rate and take into account the glycemic fluctuations and insulin doses [5].

Patients who receive IV insulin infusions typically require a transition to subcutaneous (SC) insulin administration when they begin consuming regular meals or are transferred to a lower-intensity level of care [5]. To prevent the recurrence of hyperglycemia or ketoacidosis during the transition period, it is important to allow an overlap of 2 to 4 hours [1,3] between the discontinuation of IV insulin and administration of SC insulin. Although several different methods of transition from IV insulin have been described [6-9], rebound hyperglycemia remains a major challenge in practice [10,11]. Rebound hyperglycemia has the potential to increase the ketone body concentration, thereby further delaying the DKA resolution, increasing the length of hospital stay, and increasing the risk of mortality and morbidity [12].

The use of SC long-acting basal insulins, such as glargine (Lantus, Sanofi-Aventis, Paris, France) and detemir (Levemir, Novo Nordisk, Bagsvaerd, Denmark), has become widespread. A relatively flat, consistent time-action profile constitutes the pharmacodynamic and pharmacokinetic component of basal insulin therapy [13]. In the last few years, degludec (Tresiba, Novo Nordisk), an ultra-long-acting, once-daily basal insulin, has also been widely used. Low day-to-day variability in the glucose-lowering effect and low rates of hypoglycemia have been observed in subjects who received degludec [14,15]. Owing to its pharmacokinetic properties, initiation of a SC basal insulin therapy concurrently with CIII is recommended for management of DKA to prevent rebound hyperglycemia following discontinuation of the CIII [16].

However, concurrent basal SC insulin administration during CIII is not a widely used standard treatment. It is only mentioned based on a few small-sized randomized controlled trials (RCTs) and cohort studies in the guidelines by Joint British Diabetes Society and the British Society of Pediatrics Endocrinology and Diabetes. In addition, there is insufficient evidence to demonstrate that early administration of SC basal insulin improves the outcomes in non-DKA patients who received CIII for treating severe hyperglycemia. Severe hyperglycemia includes relatively mild conditions that do not satisfy the criteria for DKA or HHS (i.e., clinically insignificant stress ketosis or compensated DKA) [17]. CIII is also recommended for several clinical indications, including severe hyperglycemia exacerbated during high-dose glucocorticoid therapy [18] and poorly controlled DM with SC insulin injections [19].

The primary objective of this study was to evaluate the incidence of rebound hyperglycemia during the transition period according to the early administration of SC basal insulin with CIII in patients with severe hyperglycemia. The secondary objectives were to evaluate the length of hospital stay, incidence of hypoglycemia, and difference in the blood glucose levels at the time of transition according to the early administration of SC basal insulin with CIII.

METHODS

Subjects

This retrospective observational study was conducted at the Seoul National University Bundang Hospital (SNUBH), a 1,300-bed teaching hospital in South Korea. Subjects aged >18 years with severe hyperglycemia, who were admitted to SNUBH and received CIII between January 1, 2018 and January 31, 2021, were identified. Subjects were excluded if they were discharged or transferred within 24 hours of CIII discontinuation or if they had other indications for insulin therapy (e.g., requiring surgery) within 48 hours of CIII discontinuation. Subjects were also excluded if: CIII was not changed to the multiple SC insulin injection (MSII) regimen, CIII was discontinued with a blood glucose level of >250 mg/dL, or dextrose fluid infusion was continued during MSII. We identified 234 subjects who were treated under the CIII regimen for severe hyperglycemia, including the conditions that did not satisfy the criteria for DKA or HHS, between January 1, 2018 and January 31, 2021. Among these subjects, 165 were included in the final analysis (Fig. 1). The study design was approved by the SNUBH Institutional Review Board (No. B-2102-669-101), and informed consent was waived owing to the retrospective nature of this study.

Insulin administration

Following the administration of an initial IV rapid-acting insulin analog dose (0.1 units/kg), CIII was performed. The rate of insulin infusion was controlled by the algorithm. After CIII was started; it is recommended to commence once daily 0.25 units/kg body weight of SC long-acting basal insulin (Lantus, Levemir, or Tresiba) (Supplemental Table S1). The subjects were divided into two groups. The early basal insulin group was defined as subjects who received the first SC basal insulin started within

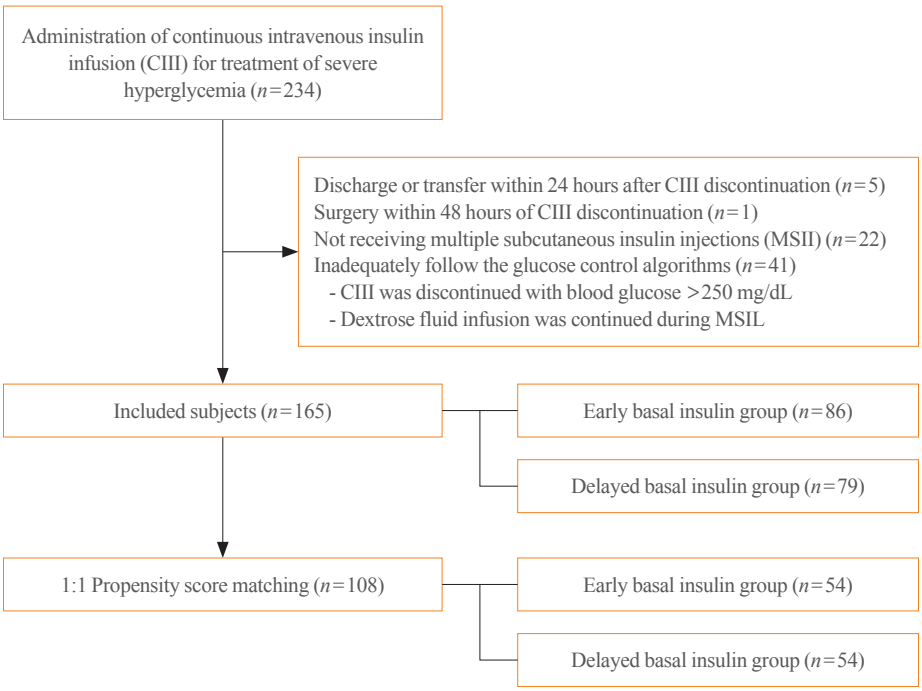

Fig. 1. Flow chart of patient enrollment. Among identified 234 subjects, 165 subjects were finally included. MSII, multiple subcutaneous insulin injection.

24 hours of CIII initiation and ≥4 hours before discontinuation. The delayed basal insulin group was defined as subjects who were not classified in the early basal insulin group. In both groups, for patients whose blood glucose level decreased below 250 mg/dL, 5% or 10% dextrose fluid was administered intravenously. If the subject was eating normally and stable blood glucose levels were achieved, MSII was initiated and recommended to be overlapped with CIII for 2 hours if a long-acting basal insulin had not yet started according to the SNUBH insulin transition algorithm (Supplemental Table S2).

Outcomes of interest

The primary outcome of this study was the incidence of rebound hyperglycemia after CIII discontinuation. Since it is recommended that the rate of IV insulin administration be adjusted to maintain glucose values between 150 and 200 mg/dL in DKA or 250 and 300 mg/dL in HHS until they are resolved [2], rebound hyperglycemia was defined as a blood glucose level of >250 mg/dL in 24 hours following CIII discontinuation. Capillary blood glucose levels were collected up to 24 hours following CIII discontinuation and categorized into four 6-hour intervals as follows: 1–6, 7–12, 13–18, and 19–24 hours. The secondary outcomes were the incidence of hypoglycemia, length of hospital stay, and difference in the blood glucose levels at the time of transition. Hypoglycemia was defined as any blood glucose level of <70 mg/dL during CIII or 24 hours following discontinuation. The length of hospital stay was defined as the time from admission to discharge, including the time spent in the emergency department. Subjects who were transferred to another unit or hospital for clinical indications other than glucose control (i.e., rehabilitation or surgery) were excluded from this analysis (n=21). The difference in the blood glucose levels at the time of transition was defined as the difference between the glucose levels immediately before and after CIII discontinuation.

Other measurements

Data on demographic information, including type and duration of DM, and precipitating factors in the development of severe hyperglycemia, including the usage of steroids, were obtained from electronic medical records. In addition, information on inpatient management, such as the use of insulin, intravenous fluids, as well as information regarding laboratory values, length of hospital stay, and inpatient mortality were also obtained.

Statistical analyses

Continuous variables are presented as the mean±standard deviation (SD). Categorical variables are expressed as numbers and percentages. To reduce the possible impacts of a selection bias

and of potential confounding factors that can arise in an observational study, propensity score matching (PSM) was performed to adjust differences in patient characteristics. Patients who received early basal insulin injection were matched 1:1 to those with a similar propensity score who did not receive early basal insulin injection using a nearest neighbor-based approach algorithm (caliper width: 0.2 SDs of the propensity score logit [20-23]). Continuous variables were compared between groups using the Mann–Whitney *U* test, and categorical variables were compared between groups using Fisher's exact test. Logistic regression analyses were performed to estimate odds ratios with 95% confidence intervals (CIs), with the incidence of rebound hyperglycemia being the outcome variable. The early basal insulin group was additionally compared to the delayed basal insulin group consisting only patients who had overlapped administration of basal insulin and CIII. In addition, we performed subgroup analysis according to the classification of severe hyperglycemia (DKA or HHS vs. non-DKA or HHS). Differences in the blood glucose levels at the time of transition and the length of hospital stay were assessed using linear regression analyses. Finally, we performed multivariable analyses, adjusted for all the covariates that were known to influence the blood glucose levels or length of hospital stay. The significance threshold was set at 2-sided $P<0.05$. All the analyses were performed using R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population and baseline characteristics

The subjects' clinical characteristics at the time of admission are shown in Table 1. The mean age was 60.4±19.9 years and 60 (36.4%) subjects were women. The mean body mass index (BMI) and glycated hemoglobin levels were 23.5±5.3 kg/m^2 and 11.0%±2.7% (96.6±29.6 mmol/mol), respectively. Among all the subjects, 62 (37.6%) were newly diagnosed with DM. The severe hyperglycemia included DKA (24.8%), HHS (19.4%), HHS with ketoacidosis (30.3%), and severe hyperglycemia that did not satisfy the criteria for DKA or HHS (25.5%). The diagnoses of DKA and HHS were based on the American Diabetes Association diagnostic criteria [2]. Severe hyperglycemia occurred in 41 subjects (24.8%), due to non-adherence to treatment with oral hypoglycemic agents or inappropriate use of insulin. In 63 (38.2%) and subjects, concomitant acute disease (i.e., infection, myocardial infarction, or acute stroke) was diagnosed. The presence of acute diseases appeared to trigger the occurrence of severe hyperglycemia. Among the 165 subjects, 86 and 79 were classified in the early and delayed basal insulin group, respectively. The early and delayed basal insulin groups had similar characteristics; however, subjects in the delayed basal insulin group were more likely to use steroid and had lower serum osmolality levels. After matching with the estimated propensity score, 54 were classified into each group. The distribution of the measured baseline covariates showed no significant differences between the early and delayed basal insulin groups. Matched variables that may affect the incidence of rebound hyperglycemia are presented in Supplemental Table S3.

Inpatient glucose management

Subjects in the early basal insulin group received their first basal insulin dose 2.0±5.5 hours following CIII initiation, whereas the delayed basal insulin group received their first basal insulin dose 29.4±24.1 hours following CIII initiation (Table 2). In the early basal insulin group, all the subjects received SC basal insulin ≥4 hours before the discontinuation of CIII. In the delayed basal insulin group, 28 (35.4%) subjects received SC insulin 1 to 2 hours before CIII discontinuation, 20 (25.3%) at the time of CIII discontinuation, and 31 (39.1%) after CIII discontinuation. The mean lengths of CIII (36.4±29.7 hours vs. 30.3±24.3 hours, $P=0.136$) and the blood glucose levels immediately before CIII discontinuation (177.1±40.9 mg/dL vs. 168.9±45.9 mg/dL, $P=0.296$) did not differ between the early and delayed basal insulin groups. Both groups had similar initial daily doses of basal insulin of approximately 17 U ($P=0.660$). Approximately, 4.7±1.1 and 4.8±1.4 of blood glucose samples were analyzed during the 24-hour period following CIII discontinuation in the early and delayed basal insulin groups, respectively ($P=0.977$). The incidence of hypoglycemia did not significantly differ between the early and delayed basal insulin groups (5.8% vs. 5.1%, $P=1.00$). In the matched set obtained by PSM, there were no significant differences between the two groups: mean lengths of CIII, blood glucose levels immediately before CIII discontinuation, initial daily doses of basal insulin, and incidence of hypoglycemia.

Outcomes of interest

The incidence of rebound hyperglycemia was significantly lower in the early basal insulin group than in the delayed basal insulin group (54.65% vs. 86.08%, $P<0.001$). When the blood glucose measurements were categorized into four 6-hour intervals, the rate of rebound hyperglycemia was lower in the early basal insulin group than in the delayed basal insulin group during the

Table 1. Clinical Characteristics of the Patients at Admission

Variable	Before propensity score matching				After propensity score matching			
	Total (*n*=165)	Early basal insulin group (*n*=86)	Delayed basal insulin group (*n*=79)	*P* value	Total (*n*=108)	Early basal insulin group (*n*=54)	Delayed basal insulin group (*n*=54)	*P* value
Age, yr	60.4±19.9	59.3±21.0	61.6±18.6	0.464	59.9±20.0	58.8±20.3	60.9±19.9	0.596
Female sex	60 (36.4)	29 (33.7)	31 (39.2)	0.464	38 (35.2)	18 (33.3)	20 (37)	0.840
Height, cm	163.9±10.4	165.4±10.4	162.2±10.2	0.074	164.3±10.0	164.5±10.3	164.0±9.7	0.797
Weight, kg	63.4±19.8	65.7±23.0	60.8±15.3	0.326	63.7±19.8	64.0±23.3	63.4±15.7	0.886
BMI, kg/m^2	23.5±5.3	24.0±5.8	23.0±4.6	0.417	23.6±5.3	23.8±5.8	23.5±4.8	0.820
Previous DM treatment				0.451				0.816
None	62 (37.6)	36 (41.9)	26 (32.9)		41 (38)	21 (38.9)	20 (37)	
Insulin	39 (23.6)	20 (23.3)	19 (24.1)		22 (20.4)	12 (22.2)	10 (18.5)	
OHA	64 (38.8)	30 (34.9)	34 (43.0)		45 (41.7)	21 (38.9)	24 (44.4)	
Metformin	49 (31.6)	22 (28.2)	27 (35.1)	0.456	32 (31.4)	13 (26.5)	19 (35.8)	0.424
Sulfonylurea	36 (23.3)	18 (23.1)	18 (23.4)	1.000	21 (20.6)	10 (20.4)	11 (20.8)	1.000
DPP4 inhibitor	49 (31.6)	21 (26.9)	28 (36.4)	0.275	30 (29.4)	13 (26.5)	17 (32.1)	0.692
SGLT2 inhibitor	8 (5.2)	5 (6.4)	3 (3.9)	0.731	6 (5.9)	4 (8.2)	2 (3.8)	0.603
Other OHA	9 (5.8)	5 (6.4)	4 (5.2)	1.000	6 (5.9)	3 (6.1)	3 (5.7)	1.000
Classification of DM				0.198				0.875
Type 1 DM	14 (8.5)	9 (10.5)	5 (6.3)		9 (8.3)	4 (7.4)	5 (9.3)	
Type 2 DM	138 (83.6)	73 (84.9)	65 (82.3)		90 (83.3)	46 (85.2)	44 (81.5)	
Other specific type	13 (7.9)	4 (4.7)	9 (11.4)		9 (8.3)	4 (7.4)	5 (9.3)	
Duration of DM, yr	8.4±9.9	8.6±10.1	8.3±9.7	0.872	8.3±9.9	9.5±10.5	7.1±9.3	0.231
Noncompliance	41 (24.8)	24 (27.9)	17 (21.5)	0.442	25 (23.1)	16 (29.6)	9 (16.7)	0.171
Precipitating factor	63 (38.2)	30 (34.9)	33 (41.8)	0.454	40 (37)	19 (35.2)	21 (38.9)	0.842
Current steroid use	26 (15.9)	8 (9.3)	18 (23.1)	0.028[a]	14 (13)	7 (13)	7 (13)	1.000
Classification of severe hyperglycemia				0.151				0.912
DKA	41 (24.8)	20 (23.3)	21 (26.6)		33 (30.6)	17 (31.5)	16 (29.6)	
HHS	32 (19.4)	17 (19.8)	15 (19.0)		22 (20.4)	11 (20.4)	11 (20.4)	
HHS with ketoacidosis	50 (30.3)	32 (37.2)	18 (22.8)		28 (25.9)	15 (27.8)	13 (24.1)	
Non-DKA or HHS	42 (25.5)	17 (19.8)	25 (31.6)		25 (23.1)	11 (20.4)	14 (25.9)	
Admission to ICU	17 (10.3)	8 (9.3)	9 (11.4)	0.853	9 (8.3)	4 (7.4)	5 (9.3)	1.000
Initial laboratory values								
pH	7.28±0.16	7.27±0.16	7.30±0.15	0.263	7.28±0.15	7.27±0.15	7.29±0.16	0.415
Bicarbonate, mmol/L	17.9±8.5	17.1±8.4	18.7±8.6	0.255	17.93±8.89	17.2±8.6	18.7±9.22	0.407
Glucose, mg/dL	630.3±276.9	660.2±275.0	597.8±276.9	0.149	641.8±290.0	658.8±292.7	624.9±289.1	0.546
BUN, mg/dL	40.5±28.3	39.7±27.6	41.3±29.3	0.723	37.8±24.2	39.9±28.4	35.6±19.2	0.363
Creatinine, mg/dL	2.1±1.6	1.9±1.1	2.2±1.9	0.223	2.0±1.3	2.1±1.3	1.9±1.3	0.434
HbA1c, %	11.0±2.7	11.3±2.5	10.6±2.9	0.091	10.9±2.8	11.1±2.3	10.8±3.2	0.543
HbA1c, mmol/mol	96.6±29.6	100.3±27.2	92.4±31.8	0.070	96±30.2	97.8±25.1	94.2±34.8	0.435
C-peptide, ng/mL	2.2±2.6	2.1±2.9	2.3±2.3	0.586	2.2±2.7	2.1±2.9	2.2±2.5	0.890
β-Hydroxybutyrate, mmol/L	1.5±1.6	1.7±1.8	1.3±1.4	0.247	1.4±1.6	1.5±1.8	1.4±1.4	0.856
Osmolality, mOsm/kg	331.6±64.4	337.2±36.7	325.3±30.8	0.034[a]	328.5±34.9	333.2±38.7	324.2±30.7	0.204

Values are expressed as mean±standard deviation or number (%).
BMI, body mass index; DM, diabetes mellitus; OHA, oral hypoglycemic agent; DPP4, dipeptidyl peptidase 4; SGLT2, sodium/glucose cotransporter 2; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; ICU, intensive care unit; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin.
[a]Values are statistically significant ($P<0.05$) by Fisher's exact test or Mann-Whitney *U* test for categorical or continuous variables, respectively.

Table 2. Comparison of Inpatient Management by Group

Variable	Before propensity score matching			After propensity score matching		
	Early basal insulin group (n=86)	Delayed basal insulin group (n=79)	P value	Early basal insulin group (n=86)	Delayed basal insulin group (n=79)	P value
Administration interval between CIII initiation and the first basal insulin, hr	2.0±5.5	29.4±24.1	<0.001[a]	1.4±5.0	28.4±26.1	<0.001[a]
Duration of CIII, hr	36.4±29.7	30.3±24.3	0.136	35.3±31.0	29.9±26.6	0.270
Glucose level immediately before CIII discontinuation, mg/dL	177.1±40.9	168.9±45.9	0.296	175.2±39.6	168.2±44.0	0.391
First dose of subcutaneous basal insulin, U	16.6±5.6	16.7±8.1	0.660	16.4±5.7	18.6±8.9	0.137
No. of blood glucose sample[b]	4.7±1.1	4.8±1.4	0.977	4.7±1.0	4.8±1.3	0.584
Hypoglycemia[c]	5 (5.8)	4 (5.1)	1.000	3 (5.6)	2 (3.7)	1.000

Values are expressed as mean±standard deviation or number (%).
CIII, continuous intravenous insulin infusion.
[a]Values are statistically significant (P<0.05) by Mann-Whitney U tests; [b]During 24 hours after CIII discontinuation; [c]P value was calculated using a Fisher's exact test.

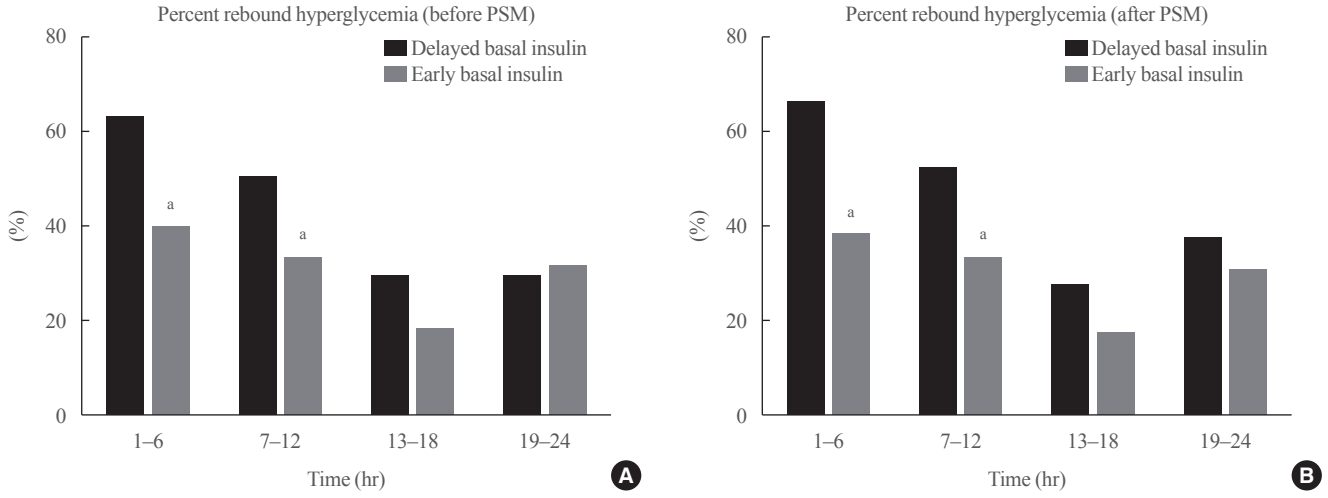

Fig. 2. Incidence of rebound hyperglycemia stratified by 6 hours intervals (A) before and (B) after propensity score matching (PSM). The rate of rebound hyperglycemia was lower in the early basal group than in the delayed basal group during the first 12 hours. [a]Statistically significant (P<0.05) by Fisher exact tests.

first 12 hours (Fig. 2). Therefore, multivariable logistic regression analyses were performed while adjusting for all the well-known factors that could affect rebound hyperglycemia. The odds of rebound hyperglycemia were 0.16 (95% CI, 0.06 to 0.43; P<0.001) and 0.14 (95% CI, 0.04 to 0.47; P=0.001) according to the subjects' group classification (early vs. delayed basal insulin group), before and after PSM, respectively (Table 3). Furthermore, the early basal insulin group had a 0.23-fold (95% CI, 0.08 to 0.67; P=0.007) risk of rebound hyperglycemia than the delayed basal insulin group consisting only patients who had overlapped administration of basal insulin and CIII (Supplemental Table S4). High glucose levels immediately before CIII discontinuation were also associated with an increased incidence of rebound hyperglycemia. In subgroup analyses, the incidence of rebound hyperglycemia was still lower in the early basal insulin group in subjects in both subgroups (DKA or HHS and non-DKA or HHS) (Supplemental Table S5).

The average difference in the blood glucose levels at the time of transition was lower in the early basal insulin group than in the delayed basal insulin group. Multivariable logistic regression analyses were performed while adjusting for all the well-known factors that could affect the blood glucose level difference. The

Table 3. Comparison of the Incidence of Rebound Hyperglycemia by Group

Variable	Before propensity score matching		After propensity score matching	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Univariable				
Group[a]	0.20 (0.09–0.42)	<0.001[b]	0.19 (0.07–0.47)	<0.001[b]
Multivariable				
Group[a]	0.16 (0.06–0.43)	<0.001[b]	0.14 (0.04–0.47)	0.001[b]
Age	0.99 (0.96–1.02)	0.499	0.99 (0.95–1.03)	0.480
Body mass index, kg/m^2	1.10 (0.98–1.26)	0.146	1.14 (0.96–1.35)	0.132
Classification (DKA)	0.72 (0.17– 2.99)	0.648	0.38 (0.06–2.45)	0.306
Classification (HHS)	0.97 (0.24–3.89)	0.969	0.95 (0.16–5.73)	0.952
Classification (DKA with ketoacidosis)	0.53 (0.15–1.94)	0.339	0.55 (0.10–3.18)	0.507
Dose of basal insulin, U	1.10 (0.97–1.25)	0.155	1.09 (0.95–1.27)	0.223
Duration of CIII, hr	0.98 (0.96–1.00)	0.064	0.98 (0.96–1.00)	0.081
Glucose level immediately before CIII discontinuation, mg/dL	1.02 (1.01–1.03)	0.005[b]	1.02 (1.00–1.03)	0.049[b]
Duration of DM, yr	1.00 (0.95–1.06)	0.876	1.00 (0.93–1.08)	0.942
Precipitating factor	2.30 (0.80–6.57)	0.120	2.10 (0.58–7.58)	0.258
OHA (metformin)	1.15 (0.34–3.93)	0.181	2.32 (0.47–11.48)	0.304
OHA (sulfonylurea)	1.13 (0.34–3.71)	0.842	0.59 (0.12–2.85)	0.512
OHA (DPP4 inhibitor)	0.46 (0.13–1.65)	0.231	0.29 (0.05–1.57)	0.151
OHA (SGLT2 inhibitor)	0.89 (0.13–5.98)	0.906	2.56 (0.26–25.6)	0.425

CI, confidence interval; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; CIII, continuous intravenous insulin infusion; DM, diabetes mellitus; OHA, oral hypoglycemic agent; DPP4, dipeptidyl peptidase 4; SGLT2, sodium/glucose cotransporter 2.
[a]Early vs. delayed basal insulin group; [b]Values are statistically significant (P<0.05) by logistic regression analyses.

early basal insulin group showed smaller differences in the blood glucose levels at the time of transition than the delayed basal insulin group, before and after PSM (P<0.001) (Table 4).

The average blood glucose level within the initial 24-hour period after CIII discontinuation was significantly lower in the early basal insulin group than in the delayed basal insulin group (205.5±62.0 mg/dL vs. 255.8±79.8 mg/dL, P<0.001). When the blood glucose measurements were categorized into four 6-hour intervals, the average blood glucose level in the early basal insulin group was lower in the first 18 hours, before and after PSM (Fig. 3).

In the univariable analyses, the mean length of hospital stay was shorter in the early basal insulin group than in the delayed basal insulin group (8.5±3.4 days vs. 9.6±3.3 days, P=0.046). When adjusting for all the well-known factors that may affect length of hospital stay, the early basal insulin group still had a shorter length of hospital stay than the delayed basal insulin group (P=0.027). Presence of precipitating factors and classification of HHS of severe hyperglycemia were associated with a longer length of hospital stay (Table 4).

DISCUSSION

In this study, we demonstrated that the early co-administration of SC long-acting basal insulin from the initiation of CIII in subjects with severe hyperglycemia was associated with a reduced incidence of rebound hyperglycemia without increasing the occurrence of hypoglycemia. In addition, subjects in the early basal insulin group had a lesser difference in the blood glucose levels at the time of transition and lower mean blood glucose levels following CIII discontinuation than those in the delayed basal insulin group. Moreover, we showed a shorter length of hospital stay in the early basal insulin group, after adjusting for the covariates.

The administration of SC basal insulin from the initiation of CIII was previously reported as a treatment strategy to prevent rebound hyperglycemia in patients with DKA. One study showed that a daily injection of glargine at 0.25 U/kg body weight was associated with a lower rate (33.3% vs. 93.5%, P<0.001) of rebound hyperglycemia during the 12-hour follow-up period [10]. Another study showed that an injection of

Table 4. Comparisons of the Differences in Blood Glucose Levels at the Time of Transition and the Length of Hospital Stay by Group

Variable	Difference in glucose levels before PSM (n=165)		Difference in glucose levels after PSM (n=108)		Length of hospital stay (n=144)	
	B±SE	P value	B±SE	P value	B±SE	P value
Univariable						
Group[a]	–79.92±15.34	<0.001[b]	–84.83±18.76	<0.001[b]	–1.13±0.56	0.046[b]
Multivariable						
Group[a]	–84.61±22.88	<0.001[b]	–84.59±25.76	0.001[b]	–1.20±0.53	0.027[b]
Age, yr	–0.29±0.49	0.562	–0.86±0.62	0.169	–0.00±0.02	0.837
BMI, kg/m^2	3.19±2.02	0.117	1.54±2.37	0.519	-	-
Classification (DKA)[c]	–27.80±22.91	0.227	–35.76±27.97	0.204	0.52±0.78	0.505
Classification (HHS)[c]	–27.09±23.40	0.249	–33.38±28.48	0.244	1.64±0.81	0.043[b]
Classification (HHS with ketoacidosis)[c]	–14.423±22.26	0.518	–21.64±27.85	0.439	0.38±0.75	0.613
Dose of basal insulin, U	–0.66±1.53	0.669	0.38±1.71	0.825	-	-
Duration of CIII, hr	–0.27±0.41	0.511	–0.42±0.44	0.353	0.02±0.01	0.056
Glucose level immediately before CIII discontinuation, mg/dL	–0.90±0.19	<0.001[b]	–0.96±0.23	<0.001[b]	-	-
Duration of DM, yr	0.63±0.86	0.467	1.85±1.07	0.085	–0.03±0.03	0.390
Precipitating factor	–27.92±17.33	0.109	–22.10±20.55	0.285	2.11±0.63	0.001[b]
OHA (metformin)	3.79±22.97	0.869	–0.95±27.07	0.972	-	-
OHA (sulfonylurea)	9.41±23.13	0.685	14.73±28.66	0.609	-	-
OHA (DPP4 inhibitor)	–1.55±23.70	0.948	–24.65±28.47	0.389	-	-
OHA (SGLT2 inhibitor)	3.71±40.16	0.927	21.15±45.66	0.645	-	-

B, β coefficient; SE, standard error; PSM, propensity score matching; BMI, body mass index; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; CIII, continuous intravenous insulin infusion; DM, diabetes mellitus; OHA, oral hypoglycemic agent; DPP4, dipeptidyl peptidase 4; SGLT2, sodium/glucose cotransporter 2.
[a]Early vs. delayed basal insulin group; [b]Values are statistically significant (P<0.05) by linear regression analyses; [c]Data are compared to the category of severe hyperglycemia that did not satisfy the criteria for either DKA or HHS.

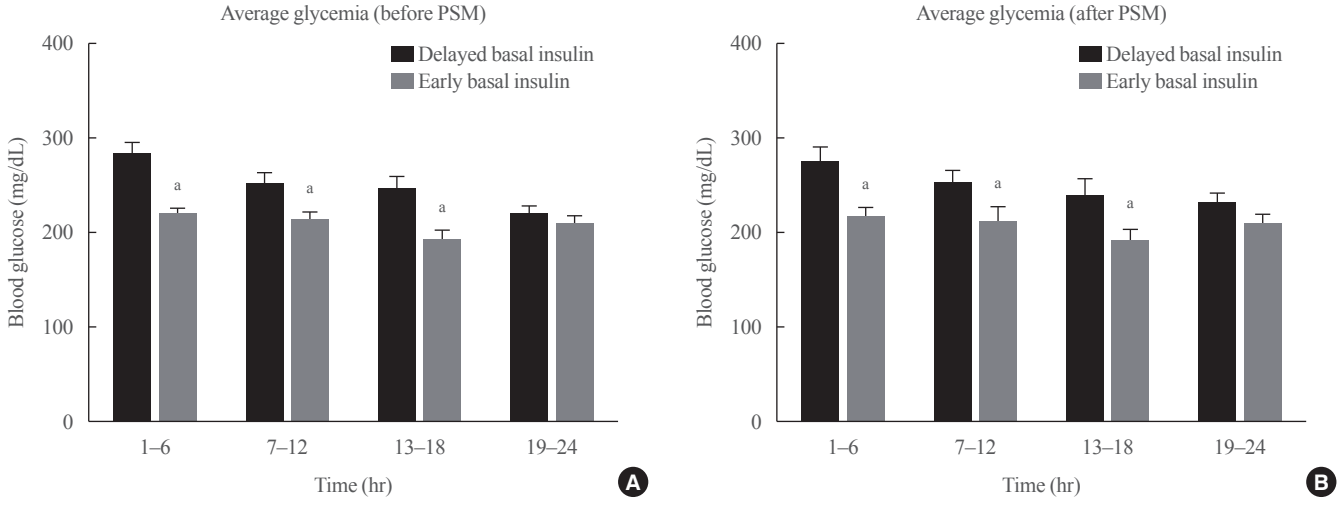

Fig. 3. Average glucose level categorized into four 6-hour intervals (A) before and (B) after propensity score matching (PSM). Data presented as mean±standard error of the mean. The average blood glucose levels were lower in the first 18 hours. [a]Statistically significant (P<0.05) by Mann-Whitney U tests.

glargine at 0.4 U/kg body weight was associated with a lower rate (35% vs. 51%, $P=0.046$) of rebound hyperglycemia during the 24-hour period following CIII discontinuation [24]. In the present study, the incidence of rebound hyperglycemia was lower in the early basal insulin group than in the delayed basal insulin group during the 24 hours after CIII discontinuation, which is consistent with the findings of previous studies [10,24]. In previous studies, basal insulin administered within 3 [24], 12 [10], or 24 [25] hours of CIII initiation were considered safe and efficacious in the treatment of patients with DKA. In addition, basal insulin administered ≥4 hours before CIII discontinuation was well tolerated and convenient [26]. Therefore, the time threshold in the early basal insulin group in our study was chosen, according to the pharmacokinetics of long-acting basal insulin, to ensure an identifiable overlap of the action of SC basal insulin with that of CIII [27,28].

In this study, the lower incidence of rebound hyperglycemia of the early basal insulin group could be attributed to the low average difference in the blood glucose levels at the time of transition and the low mean blood glucose levels following CIII discontinuation. After adjusting for all well-known covariates that may affect rebound hyperglycemia, the incidence of rebound hyperglycemia was still lower in the early basal insulin group than in the delayed basal insulin group. In addition, this relationship did not change in subgroup analysis excluding subjects who received SC basal insulin after CIII discontinuation. It has been reported that the variables predictive of an unsuccessful transition were old age, high doses of IV insulin, and wide blood glucose level variations in the 24-hour period before insulin infusion was discontinued [7]. In the present study, the variables associated with rebound hyperglycemia were high BMI and short duration of CIII in the univariable analysis.

In this study, 45% of subjects were identified as having severe hyperglycemia without ketoacidosis. Therefore, we could demonstrate that early SC basal insulin administration is effective not only for patients with DKA but also for non-DKA patients who received CIII for treating severe hyperglycemia. When patients presented with severe hyperglycemia, several hours were required to distinguish DKA from other diseases that could present as severe hyperglycemia. Moreover, the treatment generally follows the same principles [17], since there are few guidelines, which differentiate the management of HHS from that of DKA [29]. Therefore, it may be more practical to assess the efficacy of the early administration of basal insulin with CIII for treating not only DKA but also other severe hyperglycemic conditions. In fact, subjects diagnosed with neither DKA nor HHS and received early SC basal insulin showed lower incidence of rebound hyperglycemia in the subgroup analysis of our study. One previous study showed that the concurrent initiation of glargine reduced rebound hyperglycemia in patients receiving IV insulin infusion for the management of hyperglycemia associated with organ transplantation, other surgeries, or infections [10]. Another study indicated that glargine administered once per day reduced the duration of insulin infusion in patients who do not have DM and developed hyperglycemia after cardiac surgery [30].

Hypoglycemic events were not more prevalent in the early basal insulin group than in the delayed basal insulin group in our study before and after PSM, and this result is consistent with that of previous studies [10,24,25,31]. Thus, the co-administration of use of SC basal insulin early with CIII appears to be safe for treating patients with severe hyperglycemia.

In this study, we showed that the early administration of SC basal insulin of 0.25 U/kg with CIII was associated with a shorter length of hospital stay. Since hospital stay is associated with various covariates, we adjusted all covariates that were well-known factors that could affect length of hospital stay: age, classification of severe hyperglycemia diagnosis, CIII duration, concomitant acute disease, and duration of DM. Since the addition of once daily basal insulin for the subjects on CIII did not shorten the length of infusion in our study, the lower rates of rebound hyperglycemia may have resulted in proper glycemic control following CIII discontinuation, leading to shorter hospital stays. Several previous studies evaluated the length of hospital stay in adult patients with DKA; however, no study has demonstrated the difference in the length of hospital stay for patient's undergoing co-administration of SC basal insulin and CIII [24,25,31]. To the best of our knowledge, this is the first study to show a shorter hospital stay in subjects who received concomitant basal insulin and IV insulin infusion.

Nevertheless, some findings should be interpreted with caution. First, owing to the retrospective nature of this study, subjects were not randomized to receive either early or delayed basal insulin therapy. Although we added analyses using the PSM method adjusted for all potentially clinical relevant covariates when performing multivariable analyses, the association between shorter length of hospital stay and early basal insulin administration should be confirmed in large RCTs. Second, although the SNUBH algorithms for the administration of CIII and SC insulin remained consistent throughout the study period, instances of inadequately followed algorithms occurred. Since our study included subjects with severe hyperglycemia treated

with CIII, the mean age of the subjects was considerably older than those of previous studies [24,25,31], which included subjects exclusively with DKA. It is assumed that the primary physicians attempted to regulate the SC insulin dose to levels that were lower than those stipulated in our hospital algorithms to avoid any hypoglycemic events in older patients with severe hyperglycemia. These practice deviations may have increased the mean blood glucose level above the recommended target range of 140 to 180 mg/dL [1] after CIII discontinuation. Finally, since randomized controlled studies and retrospective studies exist on a similar topic, it is difficult to distinguish this study from previous studies. However, there are not many related studies that have evaluated the effect of early administration of SC basal insulin on reducing rebound hyperglycemia in patients without DKA. Therefore, this study subject can still be meaningful as additional evidence.

In conclusion, early co-administration of basal insulin with CIII prevents rebound hyperglycemia and shortens the length of hospital stay without increasing the hypoglycemic events in patients with severe hyperglycemia.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This work was supported by grant number: 14-2019-027, from the SNUBH Research Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors thank Division of Statistics in Medical Research Collaborating Center at Seoul National University Bundang Hospital for statistical analysis.

AUTHOR CONTRIBUTIONS

Conception or design: Y.L., J.J., Y.H.J., H.C.J. Acquisition, analysis, or interpretation of data: Y.L., J.H.O., H.S.P., H.W.K., J.L., E.S.K., N.H.K. Drafting the work or revising: Y.L., J.R., S.K., J.H.C., H.C.J. Final approval of the manuscript: Y.L., H.C.J.

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