

Comparison of Glycemic Control between Continuous Regular Insulin Infusion and Single-dose Subcutaneous Insulin Glargine Injection in Medical Critically Ill Patients

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Abstract

Background and Aims: This study aimed to compare glycemic control between continuous intravenous regular insulin infusion and single-dose subcutaneous insulin glargine injection in medical critically ill patients. **Subjects and Methods:** A prospective noninferiority study was conducted in medical critically ill patients who developed hyperglycemia and required regular insulin infusion by the Intensive Care Unit glycemic control protocol. The eligible patients were switched from the daily regular insulin requirement to single-dose subcutaneous insulin glargine injection by a 100% conversion dose. Arterial blood glucose was checked every 2 h for 24 h. Success cases were blood glucose levels of 80–200 mg/dL during the study period. The mean time-averaged area under the curves (AUCs) of blood glucose levels between the two types of insulin were compared by *t*-test. **Results:** Of 20 cases, 14 cases (70%) were successful. The mean time-averaged AUCs of blood glucose levels between the two types of insulin were not significantly different (155.91 ± 27.54 mg/dL vs. 151.70 ± 17.07 mg/dL, $P = 0.56$) and less than the predefined noninferior margin. No severe hypoglycemic cases were detected during the study period. **Conclusions:** Single-dose subcutaneous insulin glargine injection was feasibly applied for glycemic control in medical critically ill patients. The glycemic control in the critically ill patients by a single dose of subcutaneous insulin glargine was comparable to standard intravenous regular insulin infusion. A conversion dose of 100% of the daily requirement of regular insulin is suggested.

Keywords: Blood glucose, critically ill patients, glycemic control, insulin glargine, regular insulin

INTRODUCTION

Stress-induced hyperglycemia in the critically ill patient is a common metabolic disturbance which is associated with Intensive Care Unit (ICU) morbidity and mortality.^[1-3] The incidence of this glycemic disorder is approximately 30%–60% which depends on the definition and diagnosis criteria in several critically ill settings.^[1,4,5] Alteration of gluconeogenesis and insulin receptor sensitivity are among the common pathophysiologies of stress-induced hyperglycemia.^[6] Furthermore, certain ICU management strategies, including highly concentrated glucose intravenous fluid, catecholamine infusion, renal replacement therapy, and several medications, also carry the risk of developing hyperglycemia.^[5]

Glycemic control in the critically ill patient is generally recommended in standard ICU care. From a recent study and recommendation, a blood glucose level between

140 and 180 mg/dL is strongly recommended in all patients who develop acute hyperglycemia with a blood glucose level >200 mg/dL during ICU admission.^[7] The standard management protocol, including continuous regular insulin infusion with a glycemic control protocol, has demonstrated the most suitable method for blood glucose control in the ICU.^[8-12]

Insulin glargine is an insulin analog that is long acting and “peakless” which was introduced into clinical practice several years ago for blood glucose control in the outpatient setting.^[13] This specific type of insulin requires only a single daily dose

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of subcutaneous injection which is more convenient and requires fewer devices. Several studies demonstrated optimal blood glucose control with the use of insulin glargine without hypoglycemic complications, particularly in outpatients with both type-1 and type-2 diabetes mellitus (DM).^[14-16] However, the number of studies of blood glucose control by insulin glargine in the ICU setting is limited. Therefore, we aimed to conduct a comparative study of glycemic control between standard continuous regular insulin infusion and single-dose subcutaneous insulin glargine injection in critically ill patients. We hypothesized that blood glucose control by single-dose subcutaneous insulin glargine injection was not inferior to standard continuous regular insulin infusion in critically ill patients.

SUBJECTS AND METHODS

Patients

Between October 2014 and December 2015, all critically ill patients who required continuous regular insulin infusion for blood glucose control in our medical ICU were screened for inclusion in the study. The study setting was the ICU of a teaching hospital in the south of Thailand.

The criterion for inclusion in the study was the desired blood glucose level between 80 and 200 mg/dL by a constant dose of regular insulin infusion for 24 h at a constant continuous gastric feeding rate of the standard enteral formula (Nutren Optimum®, Nestle, Switzerland). Patients who were pregnant, hemodynamically unstable with a mean arterial blood pressure <65 mmHg, developed acute hyperglycemic complications, for example, diabetic ketoacidosis, hyperosmolar coma, required renal replacement therapy, or refused to participate in the study were excluded. The study protocol was approved by the ethics committee (EC) at the Faculty of Medicine, Prince of Songkla University, Thailand (EC number: 57-175-14-1). All participants or their relatives were informed and signed the consent form before entering the study.

Study protocol

The study period was 24 h. All eligible patients were switched to single-dose subcutaneous insulin glargine injection with a 1-h washout period before the transition. The dose of insulin glargine was derived from the accumulative dosage of the previous 24 h of regular insulin infusion. The 100% equivalent dose of insulin glargine (Lantus®, Sanofi-Aventis, USA) was then subcutaneously injected at the periumbilical area by critical care nurses. Arterial blood glucose was regularly measured every 2 h until 24 h by a point-of-care glucometer device (Accu-Chek Performa®, Roche diagnostics, Thailand). The rate caloric supplement by enteral route was maintained before and during the study period to keep a constant level of glucose administration.

If the blood glucose levels were between 80 and 200 mg/dL during the study period, the patients were recorded as “success patients.” The patients who failed blood glucose control

with blood glucose levels >200 mg/dL were switched back to continuous regular insulin infusion and were defined as “failure cases.” On the other hand, patients who developed severe hypoglycemia with blood glucose levels <60 mg/dL were immediately given 50 mL of 50% dextrose solution intravenously, and continuous intravenous dextrose solution infusion was started with hourly blood glucose monitoring. These cases were defined as “failure cases.” The study protocol was registered with the Thai Clinical Trial Registry (TCTR 201-6012-6004).

Data collection

All demographic data including age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, history of DM, serum creatinine, history of corticosteroid use and inotropes or vasopressor agents, days from ICU admission, and total daily caloric supplement were collected. The accumulative dosage of regular insulin in 24 h before the study period was also collected. The blood glucose levels from 24 h before and during the study period were recorded every 2 h. In addition, the success rate of glycemic control by insulin glargine and the rate of severe hypoglycemia were recorded.

Analysis

The sample size of this study was calculated by the noninferiority trial fashion. Bhurayanontachai *et al.*^[17] compared glycemic control between continuous intravenous regular insulin infusion and single-dose subcutaneous insulin glargine injection by an 80% equivalent dose of the accumulative dosage of regular insulin. They found that the difference in the mean time-averaged area under the curves (AUCs) of the blood glucose levels between the two types of insulin was 22.53 ± 33.35 mg/dL.^[17] Therefore, we assumed that the 100% equivalent dose of insulin glargine to regular insulin could control blood glucose within the noninferior margin of 22.53 ± 33.35 mg/dL. With the power of 80% to detect noninferiority and the expected drop-out rate of 20%, this study eventually required 20 patients to confirm the hypothesis. Continuous variables were expressed as mean \pm standard deviation (SD) or median with a minimum and a maximum dependent on the distribution of data and discrete variables that were expressed in percentages.

The success rate of glycemic control by insulin glargine was expressed in percentage. Because of some missing blood glucose values before conversion to insulin glargine, the time-averaged AUC of the blood glucose level was preferred and calculated as the AUC of blood glucose level divided by its total time interval. The mean time-averaged AUCs of the blood glucose level \pm SD between the types of insulin were compared by *t*-test. The differences of clinical characteristics between the success and failure cases were compared by independent *t*-test, Mann–Whitney test, Chi-square test, and Fisher’s exact test as appropriate. $P < 0.05$ was defined as statistically significant. All statistical analyses were computed by MedCalc® Statistical Software version 17.1 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Patients' data

Twenty patients were recruited into the study. The mean age was 57.75 ± 19.04 years, and 9 patients were male gender. The mean APACHE II was 17.25 ± 6.67 . The mean number of days from ICU admission to study recruitment was 7.45 ± 5.71 days. Seven patients had an underlying disease of DM and a history of corticosteroid use. Six patients required inotropes or vasopressor agents before and during the study period. The mean arterial blood pressures between the two periods were comparable and >65 mmHg. Most of the cases received enteral nutrition with a mean total daily calorie intake of 1340.15 ± 431.64 Kcal/day. The median (minimum, maximum) dose of continuous infusion of regular insulin per hour before the study period was 2 (1, 6) units/h. Subsequently, the median (minimum, maximum) daily dose of insulin glargine during the study period was 48 (24, 144) units/day.

The success rate of glycemic control of insulin glargine according to the unit protocol was 14/20 (70%). All demographic data and clinical characteristics were comparable between the success and failure cases [Table 1].

Glycemic control between types of insulin

Of the 20 patients, the mean time-averaged AUC of blood glucose level of insulin glargine was not significantly higher than continuous regular insulin infusion (155.91 ± 27.54 mg/dL vs. 151.70 ± 17.07 mg/dL, $P = 0.56$). The difference in the mean time-averaged AUCs of the blood glucose levels between the two types of insulin was -4.21 mg/dL (95% confidence interval, -18.70 – 10.46 ; $P = 0.56$), which was less than the predefined noninferior margin. The mean time-averaged AUC of blood glucose level in the success cases was lower

during the insulin glargine period compared to the continuous regular insulin infusion period but not statistically significant (142.02 ± 17.85 mg/dL vs. 152.13 ± 17.31 mg/dL, $P = 0.14$) [Table 2].

Of the 6 failure cases, the mean time-averaged AUC of blood glucose level of insulin glargine was significantly higher than the regular insulin infusion period (186.94 ± 22.21 mg/dL vs. 150.701 ± 18.07 mg/dL, $P = 0.01$) and 4 of the failure cases occurred within the first 6 h of the study period. No severe hypoglycemia cases were reported during the study period.

DISCUSSION

Glycemic control in critically ill patients is one of the basic measurements in standard ICU care. Currently, the suggested standard recommendation to control blood glucose is between 140 and 180 mg/dL in critically ill patients by continuous intravenous infusion of regular insulin during ICU admission.^[18-21] This study aimed to identify the feasibility of using an alternative method for glycemic control in the ICU by comparing blood glucose levels between two types of insulin. Insulin glargine was selected in this study because it is long acting and has a peakless property that can be applied in critically ill patients with stable blood glucose by a constant dosage of regular insulin infusion. We found that the success rate of single-dose subcutaneous insulin glargine injection with 100% equivalence to the accumulative dosage of regular insulin infusion was 70%. Although the mean time-averaged AUC of blood glucose level of the insulin glargine treatment period was higher than regular insulin infusion, this difference was not statistically significant and less than the noninferior margin.

Table 1: Clinical characteristics of success and failure cases during insulin glargine treatment

Clinical characteristics	All cases (n=20)	Success cases (n=14)	Failure cases (n=6)	P
Age (years), mean±SD	57.75±19.04	55.71±20.60	62.50±15.35	0.48*
Male sex, n (%)	9 (45)	6 (42.86)	3 (50)	0.89†
APACHE II, mean±SD	17.25±6.67	15.36±4.77	21.67±8.75	0.05*
Days from ICU admission (days), mean±SD	7.45±5.71	7.50±5.49	7.33±6.77	0.95*
History of diabetes mellitus, n (%)	7 (35)	4 (28.57)	3 (50)	0.14†
Current steroid treatment, n (%)	7 (35)	5 (35.71)	2 (33.33)	0.67†
Used of invasive ventilator, n (%)	18 (90)	12 (85.71)	6 (100)	0.23†
Inotropes/vasopressor used, n (%)	6 (30)	4 (28.57)	2 (33.33)	0.92†
Mean arterial pressure (mmHg), mean±SD	83.58±15.14	84.82±13.57	80.66±19.43	0.59*
Serum potassium (mEq/L), mean±SD	4.31±0.98	4.40±1.07	4.13±0.80	0.58*
Serum creatinine (mg/dL), mean±SD	1.79±1.75	1.67±1.92	2.07±1.36	0.65*
Total daily caloric supplement during study period (kcal/day), mean±SD	1340.15±431.64	1307.86±465.62	1410.00±369.59	0.64*
Enteral nutrition, n (%)	20 (100)	14 (100)	6 (100)	0.99†
Blood glucose at entry (mg/dL), mean±SD	156.45±34.26	160.57±30.97	146.83±42.53	0.43*
Blood glucose before insulin glargine injection (mg/dL), mean±SD	133.00±28.63	125.64±28.53	150.17±22.20	0.08*
Average regular insulin infusion per hour (units), median (minimum-maximum)	2 (1-6)	2 (1-6)	2 (1.5-3)	0.29**
Average dose of insulin glargine per day (units), median (minimum-maximum)	48 (24-144)	48 (24-144)	48 (36-72)	0.29**

*Independent t-test, **Mann-Whitney test, †Fisher exact test. APACHE II: Acute Physiologic and Chronic Health Evaluation II; ICU: Intensive Care Unit; SD: Standard deviation

Table 2: Glycemic control between regular insulin infusion and single dose of subcutaneous insulin glargine injection

Variables	Regular insulin period	Insulin glargine period	Difference	95% CI of difference	P*
All cases (<i>n</i> =20): Mean time-averaged AUC of blood glucose level (mg/dL)±SD	151.70±17.07	155.91±27.53	-4.21	-18.87-10.46	0.56
Success cases (<i>n</i> =14): Mean time-averaged AUC of blood glucose level (mg/dL)±SD	152.13±17.31	142.61±16.85	9.52	-3.75-22.79	0.15
Failure cases (<i>n</i> =6): Mean time-averaged AUC of blood glucose level (mg/dL)±SD	150.70±18.07	186.94±22.21	-36.24	-62.28-10.19	0.01

**t*-test. SD: Standard deviation; AUC: Area under the curve; CI: Confidence interval

Insulin glargine is a recombinant human insulin analog with a 1-h onset of action after subcutaneous injection, and its action continues for 24 h. Although there is no significant insulin peak, full activity is reached within 4–5 h after injection.^[13,22] Given these specific properties, insulin glargine performs as basal insulin which causes fewer hypoglycemic complications. As a result, a single daily dose of insulin glargine can give optimal glycemic control in the diabetic population. Several studies in both type-1 and type-2 DM demonstrated good glycemic control compared to NPH insulin, and fewer nocturnal hypoglycemic events were evident in the outpatient population.^[14-16,23] However, the evidence for the application of insulin glargine in the ICU is limited and inconsistent.

Schmeltz *et al.*^[24] conducted a study in hospitalized patients to identify the most appropriate dose of insulin glargine to maintain the blood glucose level between 80 and 150 mg/dL. This study group apparently found that the 80% conversion dose from the previous 6 h of regular insulin infusion to once daily dose of insulin glargine provided a 48% achievement rate of the predefined target range for the blood glucose. Datta *et al.*^[25] conducted a randomized study to compare glycemic control between the standard sliding scale of premeal regular insulin injection and once daily adjusted dose of subcutaneous injection of insulin glargine in postbariatric surgical patients. The initial dose of insulin glargine was derived from 20 times of the last dose of regular insulin (83.33% conversion dose) with a desired glycemic control range of 80–140 mg/dL. They found that insulin glargine gave a lower mean daily blood glucose concentration than the regular insulin sliding scale (134 ± 30 mg/dL vs. 154 ± 33 mg/dL, $P < 0.01$) and the rate of achievement was 60% in the insulin glargine group. Bhurayanontachai *et al.*^[17] also conducted an experimental pilot study to compare the glycemic control in 12 medical critically ill patients between regular insulin infusion and single-dose subcutaneous insulin glargine injection by 80% conversion dose from the accumulative dose of daily regular insulin requirement. Unfortunately, they found a success rate of 63.33% and a significantly higher level in the mean time-averaged AUC of blood glucose level during the insulin glargine period.^[17] Therefore, the once-daily dose of subcutaneous insulin glargine injection in stable blood glucose control was feasible, but the optimal dosage of insulin glargine needed to be identified.

Silinski *et al.*^[26] found that the dosage conversion of insulin glargine either by weight based or percentage based gave the equivalence in mean blood glucose level with a 66% success

rate of the target blood glucose of 80–140 mg/dL. Our current study demonstrated that the 100% conversion dose from the accumulative dose of daily regular insulin requirement showed a better success rate of glycemic control. However, the desired blood glucose range of 80–200 mg/dL in our study was different from the previous studies (80–150 mg/dL)^[24,25] and the current recommendation of 140–180 mg/dL.^[18]

From our findings, the failure cases tended to have higher disease severity and higher blood glucose levels before the insulin glargine injection. These results indicated that persistent severe stress or nonresolving inflammatory response in these patients may lead to poor blood glucose control by insulin glargine. However, a larger study is required to confirm this finding.

In addition to the levels of admission blood glucose, mean daily blood glucose, and peak blood glucose, the level of glycemic variability is a new index related to ICU outcome.^[27-29] Several indexes had been introduced as glycemic variability measurements such as the SD of the mean blood glucose, coefficient of variation of blood glucose, mean amplitude of glycemic excursion, and glycemic lability index. A lower glycemic variability index was associated with a better ICU outcome.^[27,29,30]

From the current study, we found that the SD of the mean time-averaged AUC of the blood glucose level during the insulin glargine period was higher than during the regular insulin infusion period. These findings represented wide glycemic variability and may result in a poor ICU outcome. The uncertain rate of drug absorption from subcutaneous tissue and alteration of pharmacodynamic and pharmacokinetic interaction in critically patients are among the possible factors that contributed to the variability of blood glucose levels from insulin glargine injection.^[31] Nevertheless, a few small studies demonstrated better glycemic control and less glycemic variability using a combination of regular insulin infusion with subcutaneous insulin glargine injection.^[32,33]

The accuracy and validity of the methods of blood glucose measurements were major considerations in blood glucose studies. Inappropriate techniques and methods can cause an exaggerated change of blood glucose values. From a recent consensus, the arterial blood glucose measured by a blood gas analyzer machine was recommended because of less error and good validity.^[34] In this study, we used a point-of-care glucometer to measure the glucose level from the arterial blood because the recent validation of this glucometer device

to measure blood glucose from arterial blood showed a very strong correlation and agreement with the standard venous blood sugar measurement.^[35]

There are some limitations of the current study. First, this is a single-center study. There are differences in the glycemic control protocols and target blood glucose levels in other centers. The current glycemic control protocol in our unit was implemented several years ago, and the desired blood glucose level is quite different from the recent recommendation. Therefore, the clinical application of our finding may be a concern. In addition, since the study period duration was 24 h, the results would be difficult to apply in current clinical practice. A longer and larger research study is required before adopting insulin glargine into critical care practice. Although the mean time-averaged AUC of blood glucose level between the two types of insulin was comparable, the major clinical outcomes such as ICU complications and mortality need to be explored. Moreover, the majority of patients in our study were clinically stable, which was evidenced by the optimal mean arterial blood pressure. The number of days from ICU admission to the time of study recruitment was more than 7 days, which was possibly in the recovery period of illness. Therefore, the application of insulin glargine in critically ill patients is essentially feasible, particularly in clinically stable and recovering patients who require minimal and constant regular insulin dosage.

CONCLUSIONS

The mean time-averaged AUC of blood glucose level between a daily single-dose subcutaneous insulin glargine injection and continuous intravenous regular insulin infusion was comparable. The efficacy of glycemic control by insulin glargine was not inferior to standard continuous regular insulin infusion. Insulin glargine can be feasibly applied for glycemic control in critically ill patients, particularly in the recovery phase of illness. The 100% conversion dose from daily regular insulin requirement was preferred. However, a larger study is needed to confirm this result and the clinical outcomes.

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Conflicts of interest

There are no conflicts of interest.

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