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RESEARCH PROTOCOL

BASal-bolus Insulin therapy in Critically ill patients (BASIC): A randomized controlled trial protocol

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ABSTRACT:

Background: Controlling blood glucose levels is crucial for optimizing outcomes in critically ill patients. While the sliding-scale insulin regimen is common, the efficacy of basal-bolus insulin therapy, using insulin glargine and insulin aspart, is less explored in critical care settings.

Objectives: This study investigates the efficacy and safety of basal-bolus insulin therapy compared to sliding-scale insulin in managing hyperglycemia in critically ill patients in a medical intensive care unit (ICU).

Methods: The BASal-Bolus Insulin Therapy in Critically Ill Patients (BASIC) trial is a single-center, open-label randomized controlled trial at Srinagarind Hospital, Thailand. The study will enroll adult critically ill patients admitted to the medical ICU with capillary blood glucose (CBG) levels between 180 and 400 mg/dL. Participants will be randomized (1:1) to receive either basal-bolus insulin therapy or sliding-scale insulin (control). The primary endpoint is the percentage of CBG within the target range of 140–180 mg/dL. The secondary outcomes include daily mean CBG levels, glucose variability index, 28-day mortality, length of stay in the ICU, incidence of nosocomial infections, ventilator-free days within 28 days, and occurrences of hypoglycemia.

Hypothesis: Basal-bolus insulin regimen has a higher efficacy in glycemic control compared to a sliding-scale regimen in critically ill medical patients.

Discussion: Evidence regarding the effectiveness of the basal-bolus insulin regimen in critically ill patients is limited, with most existing studies focusing on non-critically ill populations. This study addresses this gap by comparing the basal-bolus approach to the conventional sliding-scale insulin regimen. This trial aims to provide valuable insights into optimizing glycemic control in critically ill patients, potentially leading to improved clinical outcomes.

Ethics and dissemination: This study obtained approval from the Center for Ethics in Human Research at Khon Kaen University (Ethics Committee number: HE661013)

Trial registration: TCTR20230410009

Keywords: Basal bolus insulin; Sliding scale insulin; Critically ill patient

INTRODUCTION

Hyperglycemia in hospitalized patients is a prevalent, severe, and expensive healthcare issue with significant medical consequences. Emerging evidence suggests that hospitalized patients who encountered hyperglycemia during acute medical illness, particularly critically ill patients, were admitted to the intensive care units (ICUs). Metabolic responses to severe illness frequently result in hyperglycemia, regardless of whether the individual has a prior diagnosis of diabetes mellitus. The adaptive stress response was advantageous for survival. Hyperglycemia's pathophysiology involves increased levels of cortisol, catecholamines, glucagon, and growth hormone, along with heightened glucogenesis and glycogenolysis. Research on critically ill patients has demonstrated that hypoglycemia has been associated with unfavorable clinical results, such as increased mortality rates, more extended hospital stays, and a potentially higher risk of nosocomial infections. [1-5]

Insulin, administered intravenously through continuous infusion or subcutaneously, is the most efficient drug for promptly managing hyperglycemia in a hospital setting. Continuous insulin infusion protocols in critical care settings have proven helpful in attaining glycemic control while minimizing hypoglycemia events and enhancing hospital outcomes. [4] Subcutaneous insulin treatment, including basal-bolus regimens and sliding-scale insulin, is frequently utilized for medical and surgical patients in regular hospital wards. [2,3] Previously, there was no evidence supporting the use of subcutaneous basal-bolus insulin therapy in critically ill patients in the ICU.

OBJECTIVES

The primary objective of the BASIC study is to examine the effectiveness of basal-bolus insulin therapy with sliding-scale insulin therapy in critically ill patients with hyperglycemia admitted to medical ICUs.

MATERIALS AND METHODS

Participants

The BASIC (Basal-Bolus Insulin Therapy in Critically Ill patients) trial has been officially registered with the Thai Clinical Trials Registry under the identifier TCTR20230410009, as of April 10, 2023.

Design and setting

This trial is conducted as a single-center, superiority, randomized, open-label controlled clinical trial initiated by investigators, aiming to assess the efficacy of basal-bolus insulin therapy versus a sliding-scale regimen in critically ill patients. Recruitment of participants will occur in the medical intensive care unit (ICU) of Srinagarind Hospital, with an initiation date of April 10, 2023. Srinagarind Hospital is an academic tertiary university hospital of Khon Kaen University, Thailand. The methodology adheres to the Standard Protocol Items: Recommendations of Interventional Trials (SPIRIT) reporting guidelines (suppl file 1: Reporting checklist for protocol of a clinical trial). [6]

KEY MESSAGES:

- The BASIC trial seeks to determine whether basal-bolus insulin therapy, which involves a combination of long-acting and rapid-acting insulin, provides more effective and consistent glycemic control compared to the traditional sliding-scale insulin approach in critically ill patients. This could lead to better patient outcomes in the medical ICU setting.
- The study not only focuses on achieving target blood glucose levels but also examines a range of secondary outcomes, including glucose variability, mortality rates, ICU length of stay, incidence of nosocomial infections, ventilator-free days, and episodes of hypoglycemia.
- Current evidence on the use of basal-bolus insulin therapy in critically ill patients is sparse, as most research has been conducted in non-critically ill populations. The BASIC trial addresses this significant gap.

Ethics approval and consent

This study obtained approval from the Center for Ethics in Human Research at Khon Kaen University (Ethics Committee number: HE661013). Written informed consent was secured from each patient or from their relatives or legal representatives before they were randomized.

Eligibility criteria

The study will consider for inclusion individuals aged 18 and above who are admitted to the medical ICU of Srinagarind Hospital, Khon Kaen University, and who have a capillary blood glucose level ranging between 180-400 mg/dL.

Patients will be excluded if they meet any of the following criteria:

1. Requirement for infusion insulin
2. Ongoing continuous enteral feeding
3. Presence of shock requires vasopressors and nothing per oral
4. Raynold's phenomenon
5. Hypoglycemia prior hospital admission
6. Chronic liver disease (Child-Pugh score B and C)
7. Known history of insulin allergy or anaphylaxis,
8. Surgical patients,
9. Pregnancy
10. Inability to provide consent or lack of a legal authorized representative (LAR) within 24 hours.

Screening and randomization

Following the initial screening for eligibility, participants will be assigned in a 1:1 ratio to either the basal-bolus insulin regimen or the sliding-scale insulin regimen. This allocation uses stratified block randomization, taking into account any existing diabetes diagnosis and using block sizes of 8, 4, and 2 to ensure even distribution

among groups. The randomization sequence is created via the 'allocationTable' function in the 'redcapAPI' package.

Subsequently, the randomization process will be executed automatically by the randomization module in Research Electronic Data Capture (REDCap) version 4.3.1, hosted by Khon Kaen University.

Trial Intervention

Intervention group (Basal-bolus insulin regimen)

Upon enrollment and the acquisition of signed informed consent, participants in the basal-bolus group will stop all prior oral and injectable diabetes medications. These patients will begin an initial daily insulin regimen of 0.4 units/kg/day if their admission blood glucose levels exceed 180 mg/dL. This dose is split equally between basal insulin glargine U-100 and rapid-acting insulin aspart, with rounding rules applied based on the decimal portion. Administer insulin glargine U-100 once daily consistently each day (before breakfast or the first premeal time) and insulin aspart in three evenly split doses before every meal or four evenly split doses before enteral tube feeding. If a patient is fasting, insulin aspart is withheld. Adjustments are made the following day: insulin glargine U-100 is increased by 20% if fasting or premeal blood glucose remains above 180 mg/dL without hypoglycemia, and similarly, insulin aspart is increased if the average daily blood glucose exceeds this threshold. In cases of hypoglycemia (blood glucose below 70 mg/dL), the insulin glargine U-100 dose is reduced by 20% at the next day, and insulin aspart is withheld until blood glucose stabilizes above 140 mg/dL then restarted and decreased insulin aspart by 20% (Table 1). Supplemental insulin with insulin aspart was given in addition to the scheduled premeal insulin for CBG > 180 mg/dL per the sliding-scale protocol (Table 2). If a patient is able and expected to eat all or most of his/her meals, give insulin aspart before each meal and at bedtime, following the "usual" column. If a patient cannot eat, give insulin aspart every 6 h (6–12–6–12), following the "insulin sensitive" column. [2]

Control group (Sliding-scale insulin regimen)

Participants assigned to the sliding-scale insulin (SSI) group receive insulin aspart according to a sliding-scale protocol based on current blood glucose levels, starting at levels over 180 mg/dL (Table 2). If mean CBG at the previous day is above 180 mg/dL in the absence of hypoglycemia, increase the insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column. If a patient develops hypoglycemia (blood glucose < 70 mg/dL), hold insulin in the current meal and decrease insulin aspart in the next meal from the "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column. [2]

Both groups will receive assigned treatment until discharge from the ICU.

Assessment of drug side effects and withdrawal of intervention treatment

Following randomization, we will be made aware of the side effects of the intervention drug, especially severe hypoglycemia. We classified hypoglycemia into 3 levels (level 1 is CBG < 70 mg/dL or > 54 mg/dL, level 2 is CBG < 54 mg/dL, and level 3 is a severe event characterized by altered mental or physical status that requires assistance for treatment of hypoglycemia). The physician will evaluate the conditions for terminating the trial, including hypoglycemia level 2 (< 54 mg/dL), which is considered life-threatening and requires intravenous glucose; severe hyperglycemia (> 400 mg/dL); and major surgery that typically precludes oral intake.

Rescue therapy during hypoglycemia (CBG < 70 mg/dL), we will be giving glucose (any form of carbohydrate that contains glucose) 15-20 g orally, then CBG next 15 minutes. If there is still hypoglycemia, the threat should be repeated.

Table 1. Insulin adjustment.

Capillary blood glucose (mg/dL)	Intervention: Basal-bolus insulin	Control: Sliding-scale insulin
< 54	Withdrawal from the study	Withdrawal from the study
< 70	• Decrease dose glargine 20% (next dose) • Hold insulin aspart (bolus dose) at this premeal then decrease insulin aspart 20% (next dose), If capillary blood glucose > 140 mg/dl • Move insulin aspart (correction dose) from usual to sensitive column or resistance insulin to usual column (next dose)	• Move insulin aspart from usual to sensitive column or resistance to usual column (next dose)
70 -180	• No adjustment	• No adjustment
> 180	• If fasting or first meal glucose > 180 mg/dl, Increase dose glargine 20% (next dose) • If mean blood glucose at previous day is > 180 mg/dL, Increase insulin aspart (bolus dose) 20% (next dose) • Move insulin aspart(correction) from usual to resistance column or sensitive to usual column (next dose)	• If mean blood glucose at previous day is > 180 mg/dL, move insulin aspart from usual to resistance column or sensitive to usual column (next dose)
>400	• Withdraw from the study	• Withdraw from the study

Table 2. Supplemental correction insulin.

Capillary blood glucose (mg/dL)	Insulin sensitive	Usual	Insulin resistant
181-220	2	4	6
221-260	4	6	8
261-300	6	8	10
301-350	8	10	12
351-400	10	12	14

If capillary blood glucose < 70 mg/dL, switch usual to sensitive or resistant to usual.
If capillary blood glucose > 180 mg/dL switch sensitive to usual or usual to resistance.

OUTCOME MEASUREMENT

Primary and secondary outcomes

The primary outcome is the percentage of CBG within the range of 140–180 mg/dL. The secondary outcomes include daily mean CBG levels, glucose variability index defined as coefficient of variation of daily CBG, 28-day all-cause mortality, length of stay in the ICU, incidence of nosocomial infections, number of ventilator-free days within 28 days, and occurrences of hypoglycemia below 70 mg/dL.

DATA ANALYSIS PLAN

Sample size

In the design of our study, a crucial consideration is the determination of an appropriate sample size to detect a meaningful difference between treatment groups with sufficient statistical power. We aimed to detect a 10% difference in the mean group percentages, which based on preliminary data, indicated a mean percentage of achieving the target capillary blood glucose (CBG) level of 61% (SD = 17.7%) with a standard sliding insulin (SSI) regimen. The study is designed to have 80% power to detect the specified difference. A significance level (Alpha) of 0.05 in a two-sided test is used to assess statistical significance. The calculations accounted for a dropout rate of 20%. The calculations indicated that a total sample size of 166 patients (83 per group) is necessary to meet the study objectives.

An interim analysis was planned to ensure the efficacy and safety of the intervention after half of the patients (n=83) completed their 28-day follow-up. This interim assessment employed a symmetrical two-sided group sequential design to allow for potential early stopping for efficacy or futility. The boundaries for this interim analysis were determined using the Lan-DeMets adaptation of the O'Brien-Fleming approach, which provides stringent criteria early in the trial to control the overall type I error rate at 5%.

Data analysis

The data analysis in this clinical trial is guided by the principle of intent-to-treat (ITT). The continuous variables will be described using either means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on whether the data distribution is normal. The normality of distribution for these variables will be evaluated using the Shapiro-Wilk test. The categorical variables will be summarized with counts and percentages.

Differences in continuous variables between intervention and control groups will be tested using either the Student's T-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). The categorical variables will be analyzed using either the chi-square test for variables with sufficient expected frequencies or Fisher's exact test when cell counts are low.

The primary outcome will be assessed using the mean difference and a 95% confidence interval (95%CI) as a measure of association. In the secondary outcome analysis, the numbers of days alive without mechanical ventilator support within 28-day days will be analyzed using the Kryger Jensen and Lange test [7], which increases power for data sets with zero values. The 28-day mortality rate will be compared via Cox proportional hazards regression. All statistical analyses will be conducted using R software version 4.3.1.

The schedule of enrollment, intervention, and assessments are shown in Table 3.

DATA MANAGEMENT AND DATA MONITORING

Data collection

Data will be systematically collected using electronic case report forms (eCRFs) and entered into a specifically designed, secure Research Electronic Data Capture (REDCap) system hosted by Khon Kaen University. [8,9]

Data collection protocol includes the following baseline characteristics: age, sex, weight, height, body mass index, Charlson comorbidity index, Sequential Organ Failure Assessment (SOFA) score at 24 hours after randomization, Acute Physiology and Chronic Health Evaluation (APACHE) III score at 24 hours after randomization, time to ICU admission to randomization, the reason for ICU admission, shock at enrollment, vasopressor and steroid use at enrollment, presence of DM, blood sugar, and hemoglobin A1C.

Critical care nurses will measure CBG using the Accu-Chek Inform II system. This point-of-care device is wireless-enabled, facilitates direct data entry via touch screen

Table 3. Standard protocol items.

			Study period						
	Enrollment	Allocation	Post allocation (Daily time point)						Follow up
Timepoint	-T1	T0	D1	D2	D3	D4	D6	D7-27	D28
Enrollment									
Eligibility screen	x								
Informed consent	x								
Randomization		x							
Intervention									
Basal bolus insulin			x	x	x	x	x	x	
Sliding scale insulin			x	x	x	x	x	x	
Assessment									
Baseline data		x							
Mean percentage of CBG in range (140 - 180 mg/dL)			x	x	x	x	x	x	
Mean daily CBG			x	x	x	x	x	x	x
ICU length of stay									x
Nosocromial infection									x
Ventilator-free day in 28 days									x
Hypoglycemia < 70 mg/dL				x	x	x	x	x	

or 2D barcode reader, and integrates efficiently with electronic medical records.

Outcome variables will include incidence of nosocomial infection, duration of mechanical ventilation, ventilator-free day at day 28, ICU and hospital length of stay, all-cause ICU and hospital mortality, and 28-day mortality.

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient who has been administered an investigational intervention, regardless of causal relationship.

A serious adverse event (SAE) will include any event that results in death, requires inpatient hospitalization or prolongation of existing hospitalization, is life-threatening, or causes significant disability/incapacity. All SAEs will be meticulously documented and reported as per the regulatory requirements, irrespective of the suspected causality.

DISCUSSION

Controlling blood sugar levels in critically ill patients is an essential treatment procedure. Standard practice involves continually giving regular insulin through an intravenous infusion. [1] This approach efficiently maintains blood sugar levels within a predetermined range. This study is the initial prospective randomized clinical research that evaluates the efficacy and safety of basal-bolus insulin treatment compared to sliding-scale insulin treatment in critically ill patients admitted to a medical intensive care unit. We expect that treating with basal bolus insulin (insulin glargine and insulin aspart) will significantly enhance glycemic control compared to utilizing sliding-scale insulin treatment.

The rabbit-2 trial [2], a prospective, multicenter, randomized trial comparing the efficacy and safety of a basal-bolus insulin regimen (BBI) with sliding-scale regular insulin (SSI) in patients with type 2 diabetes, suggests that a basal-bolus insulin regimen is more effective than SSI for managing non-critically ill, hospitalized patients with type 2 diabetes in general surgical and medical wards. However, our study focused on critically ill patients admitted to the medical intensive care unit (MICU).

Limitations

This trial is a single-center randomized controlled trial involving unmasking for investigators, clinicians, and patients. Participants in the trial are selected with specific exclusion criteria, notably the exclusion of individuals in shock and those with advanced chronic liver disease. This selective exclusion is necessary due to the potential complications and differing metabolic responses that these conditions present. However, this criterion limits the applicability of the study results to a broader critically ill population that may include these conditions. We included individuals treated with corticosteroids in the trial due to their significant risk of hyperglycemia when receiving sliding-scale insulin treatment.

Trial status

At the time of submission, the BASIC trial has enrolled 65 of its planned 166 participants.

CONFIDENTIALITY
None

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None

AUTHORS' CONTRIBUTIONS
(I) Conceptualization: All authors; (II) Formal analysis: ST, AP; (III) Methodology: All authors; (IV) Project administration: ST, AP; (V) Writing – original draft: ST; (VI) Writing – review & editing: AP.

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SUPPLEMENTARY MATERIALS

Supplement Table1. Insulin treatment protocol.

A. <u>Intervention group: Basal-bolus regimen with insulin glargine and insulin aspart</u>

After signed informed consent is obtained, subjects randomized to the basal-bolus group will be:

1. Discontinue oral/injecting antidiabetic drugs on admission.
2. Start total daily insulin dose: 0.4 units/kg/day when the admission blood glucose concentration is more than 180 mg/dL
3. Give one-half of the total daily dose as insulin glargine U-100 (Lantus) and one-half as insulin aspart (Novorapid) (if the decimal portion is less than 0.5, we round down, if the decimal portion is equal or more than 0.5, we round up)
4. Give insulin glargine U-100 once daily at the same time of the day (before breakfast or first premeal time)
5. Give insulin aspart in three equally divided doses before each meal or four equally divided doses before enteral tube feeding.
6. Hold insulin aspart if patient is not able to eat.
7. Give supplemental insulin aspart following the protocol.
   (see supplement insulin table)
   - 7.1 If a patient is able and expected to eat all or most of his/her meals, give supplemental aspart before each meals following the "usual" column.
   - 7.2 If a patient cannot eat, give supplemental aspart every 6 h (6–12–6–12), following the "insulin-sensitive" column.

Insulin adjustment A

1. If the fasting or first premeal CBG during the day is > 180 mg/dl at previous day in the absence of hypoglycemia, increase the insulin glargine U-100 dose by 20% at the next day and mean blood glucose at previous day > 180 mg/dl, increase mealtime insulin aspart 20% at the next day
2. If a patient develops hypoglycemia on the previous day (< 70 mg/dL), decrease insulin glargine daily dose by 20% and hold insulin aspart until capillary blood glucose > 180 mg/dL then restart and decrease insulin aspart 20%
3. If mean blood glucose at previous day is > 180 mg/dL in the absence of hypoglycemia, increase insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column.
4. If a patient develops hypoglycemia (blood glucose < 70 mg/dL), hold insulin in the current meal and decrease insulin aspart in the next meal from "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column.

Blood glucose monitoring

Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).

B. <u>Control group: Sliding scale regimen with insulin aspart</u>

After signed informed consent is obtained, subjects randomized to the sliding-scale group will be:

1. Discontinue oral/injecting antidiabetic drugs on admission.
2. Give supplemental insulin aspart following the "sliding-scale" protocol for CBG > 180 mg/dL. (see supplement correction insulin table)
   - 2.1 If a patient is able and expected to eat all or most of his/her meals, give insulin aspart before each meal and at bedtime, following the "usual" column.

If a patient cannot eat, give insulin aspart every 6 h (6–12–6–12), following the "insulin sensitive" column.

Insulin adjustment B

1. If mean blood glucose at previous day is > 180 mg/dL in the absence of hypoglycemia, increase insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column.
2. If a patient develops hypoglycemia (blood glucose < 70 mg/dL), hold insulin in the current meal and decrease insulin aspart in the next meal from "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column.

Blood glucose monitoring

Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).