

Comparison of the Safety and Efficacy of Continuous Insulin Infusion Versus Intermittent Insulin Bolus in the Management of Hyperglycemia in Critically Ill Patients

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ABSTRACT

Objective: To compare the efficacy and safety of intravenous continuous Insulin infusion (CII) versus Intermittent Insulin Bolus (IIB) in managing blood glucose levels in critically ill patients.

Study Design: Quasi-experimental study.

Place and Duration of Study: Intensive care units (ICUs) of a tertiary care hospital from Apr to Sep 2024.

Methodology: A total of 70 critically ill patients of either sex; age ≥ 18 years and capillary blood glucose ≥ 180 mg/dL were equally distributed into CII (Group-A) and IIB (Group-B). The patients who did not survive within the first 48 hours, pregnant women, patients with hemodynamic instability (mean arterial blood pressure < 65 mmHg), necessitating renal replacement therapy or those receiving palliative care were excluded. Descriptive statistics were used to calculate percentage, frequencies and Mean $\pm$ SD. Comparison between variables were made by applying independent sample t-test along with chi-square test for categorical. The p -value of < 0.05 was considered statistically significant.

Results: There were no significant differences in baseline characteristics between the two groups. The CII (Group-A) achieved significantly lower final blood sugar levels compared to the IIB (Group-B) ($p=0.04$). The initial and final insulin doses were significantly lower in the Group-A ($p<0.001$). No significant differences were observed in hypoglycemia incidence while it was observed Group-A had a wider spread of ICU stay durations, including longer stays up to 7 days, whereas Group-B had shorter spread and more concentrated ICU stays.

Conclusion: Continuous Intravenous Insulin infusion provides superior glycemic control, reduces glucose variability, and lowers infection risk compared to Intermittent Insulin Bolus in critically ill patients. CII is associated with shorter ICU stays and improved metabolic stability.

Keywords: Critical Care, Hyperglycemia, Insulin Infusion, Intermittent insulin bolus, Intensive Care Unit.

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INTRODUCTION

Stress-induced hyperglycemia is a significant contributor to morbidity and mortality in critically ill patients, commonly occurring in the Intensive Care Unit (ICU).^{1,2} About 50 % of critically ill patients admitted in ICU can develop hyperglycemia in first 48 hours of admission.³ It is defined as transient hyperglycemia, with blood glucose levels exceeding 200 mg/dL randomly or 126 mg/dL when fasting, in individuals without pre-existing diabetes.⁴ Although more frequent in non-diabetics, stress-induced hyperglycemia can also occur in individuals with diabetes due to acute physiological stress.^{5,6}

The underlying mechanism involves the release of counter-regulatory hormones, including glucagon, growth hormone, and catecholamines, which enhance gluconeogenesis, glycogenolysis, and lipolysis leading

to hyperglycemia. Additionally, ICU interventions such as Dextrose Infusions, Vasopressors, Renal Replacement Therapy, and Corticosteroids can further exacerbate insulin resistance.^{7,8} Persistent hyperglycemia induces glycosuria and osmotic diuresis, causing dehydration, electrolyte imbalances, and hemodynamic instability, ultimately impairing wound healing and increasing the risk of complications.⁹

Optimal glycemic control is essential for improving patient outcomes, with recent guidelines recommending intervention when blood glucose exceeds 200 mg/dL during ICU admission. Two primary Insulin administration strategies are used: Continuous Intravenous Insulin Infusion (CII) and Intermittent Insulin Bolus (IIB) therapy. CII enables precise Insulin titration, facilitating tighter glycemic control, whereas IIB is easier to administer.¹⁰

Given the clinical significance of hyperglycemia management in critically ill patients, this study aims to compare the efficacy and safety of CII versus IIB. By

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evaluating glycemic control, complications, and overall patient outcomes, the findings may help optimize insulin therapy strategies and improve ICU management protocols.

METHODOLOGY

This quasi-experimental study was conducted in the intensive care units (ICUs) of a tertiary care hospital from 1 April 2024 to 30 September 2024. The study protocol was approved by the Institutional Ethical Review Board (IERB) (Approval No. 00127/24 dated Feb 2024) and informed consent was obtained from all participants or their legal representatives. Patients were enrolled using non-probability sampling. Figure shows patients enrollment process.

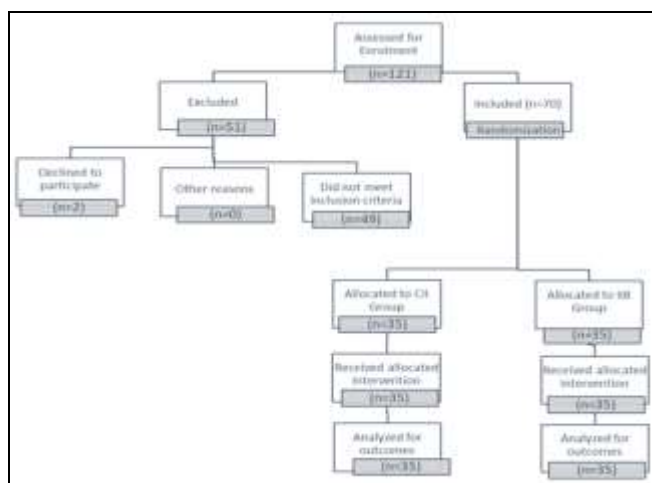


Figure: Flow diagram of patient enrollment process

The initial sample size calculation ($n=8/\text{group}$) assumed a mean glucose difference of 48 mg/dL, variance 1.73 mg/dL, $\alpha=0.05$, and 80% power. To account for potential attrition and enhance generalizability, we enrolled 35 patients per group.¹¹ The Patients were randomly assigned to two groups; Continuous Intravenous Insulin Group-A ($n=35$) and Intermittent Insulin Bolus Group-B ($n=35$) using a computer-generated randomization sequence to ensure balance in baseline characteristics and minimize selection bias. Informed consent was taken from participants before including them in the study. The following criteria was used.

Inclusion Criteria: All patients admitted in the Intensive care unit of either sex; age ≥ 18 years and capillary blood glucose $\geq 180\text{mg/dL}$ were included.

Exclusion Criteria: The patients who did not survive within the first 48 hours, pregnant women, patients with hemodynamic instability (mean arterial blood

pressure $<65\text{ mmHg}$), necessitating renal replacement therapy or those receiving palliative care were excluded.

The primary source of data was a medical record of the patient. Following parameters were noted down such as age, gender, comorbid, initial blood glucose value and initial value when starting Insulin, final blood glucose and final Insulin value when reaching target, rate of developing hypoglycemia and days elapsed since ICU admission.

Blood glucose levels were monitored using point-of-care glucose meter which was exclusively designated for this function. Patients and the doctor assessing the patient were aware of the treatment group. However, the person performing the analysis was blinded.

Continuous Intravenous Insulin Infusion (Group-A) received Insulin infusion made by dilution of 100 IU of regular in 100 ml of 0.9% Normal Saline. Insulin was administered via an infusion pump at rate of 0.05-0.01 U/kg/hr with doses titrated hourly based on blood glucose levels until stable than 2 hourly, targeting a range of 140-180 mg/dL. Target was 50-70 mg/dL reduction of blood sugar per hour.¹²

Intermittent Insulin Bolus (Group-B) received Insulin as subcutaneous or intravenous boluses every 4-6 hours, adjusted according to blood glucose levels. following sliding Insulin regimen: blood glucose at 150-200mg/dL (2-4IU bolus Insulin); 201-250mg/dL (4-6U bolus Insulin); 251-300mg/dL (6-8U bolus Insulin); and 300-350mg/dL (8-10 U bolus Insulin); $>350\text{mg/dL}$ 10+ U was used.¹²

When blood glucose (BG) fell below 70 mg/dL 15-30 g Dextrose was given and BG monitored every 15 min to keep BG $> 100\text{ mg/dL}$.

Variables were entered and analyze by Statistical Package for Social Sciences (SPSS) version-27. Descriptive statistics were used to calculate percentages, frequencies, and Mean $\pm$ SD. A Shapiro Wilk test was applied to look for non-normal data which confirmed normality for age and insulin doses ($p>0.05$), while blood glucose levels and ICU stay duration were non-normally distributed ($p<0.05$). The Mean with SD was measured for Blood Sugar levels pre and post-treatment. Comparison between variables were made by applying an independent sample t-test (e.g., for age, insulin doses) or the Mann-Whitney U test (e.g., for blood glucose, ICU days) along with the chi-square test or Fisher's exact for

categorical. The p -value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 70 patients were enrolled and equally distributed into CII (Group-A) ($n=35$) and IIB (Group-B) ($n=35$). Baseline demographics were comparable between groups (Table-I). Mean age (CII: 58.30 ± 12.40 vs. IIB: 56.70 ± 11.80 years) and gender distribution (Male: 57.10% vs. 51.40%) showed no significant differences. Further demographic distribution is shown in Table-I.

Table-I: Demographic Distribution of Study Variables ($n=70$)

Variable(s)	Group-A ($n=35$)	Group-B ($n=35$)
Age (years)	58.30 ± 12.40	56.70 ± 11.80
Gender		
Male	20(57.10%)	18(51.40%)
Female	15(42.90%)	17(48.60%)
Co-Morbid		
Type 2 Diabetes Mellitus	25(71.40%)	22(62.90%)
Hypertension	18(51.40%)	20(57.10%)
Obesity	15(42.90%)	14(40.00%)
Coronary Artery Disease	12(34.30%)	10(28.60%)
Sepsis	5(14.30%)	4(11.40%)
Type 1 Diabetes Mellitus	7(20.00%)	6(17.10%)

The results of the study showed no statistically significant difference in initial blood glucose values between the two groups ($p=0.32$). However, final blood glucose values were significantly lower in the CII group compared to the IIB group ($p=0.04$), indicating better glycemic control with continuous infusion. The initial Insulin dose was significantly higher in the IIB group (42.30 ± 10.50 IU) than in the CII group (5.20 ± 1.80 IU), with a p -value of <0.001 . Similarly, the final Insulin dose remained significantly higher in the IIB group (32.40 ± 8.60 IU) compared to the CII group (2.10 ± 0.70 IU), also with a p -value of <0.001 , is shown in Table-II.

Table-II: Comparison of Initial and Final Blood Glucose and Insulin Dose Between CII and IIB Groups ($n=70$)

Variable(s)	Group-A ($n=35$)	Group-B ($n=35$)	p -value
	Mean $\pm$ SD	Mean $\pm$ SD	
IBGV (mg/dl)	345.20 ± 45.60	338.70 ± 50.30	0.32
FBGV (mg/dl)	148.30 ± 12.70	152.60 ± 15.40	0.04
IIV (IU)	5.20 ± 1.80	42.30 ± 10.50	<0.001
FIV (IU)	2.10 ± 0.70	32.40 ± 8.60	<0.001

IBGV= initial blood glucose value, FBGV= final blood glucose value, IIV= Initial insulin value, FIV= final insulin value

The comparison of ICU stay duration between the two groups revealed a statistically significant difference ($p=0.01$). In Group-A (Continuous Insulin Infusion), the majority of patients stayed for 2 to 4 days, with a small number requiring up to 7 days. In

contrast, Group-B (Intermittent Insulin Bolus) had a higher proportion of patients staying for 3 to 4 days and none requiring more than 5 days. Notably, Group-A had a wider spread of ICU stay durations, including longer stays up to 7 days, whereas Group-B had shorter spread and more concentrated ICU stays, is shown in Table-III.

Table-III: Comparison of Number of Intensive Care Unit days Among groups ($n=70$)

	Number of ICU Days							p -value
	1	2	3	4	5	6	7	
Group-A ($n=35$)	Nil	5(7.1%)	11(15.7%)	10(14.3%)	6(8.6%)	2(2.9%)	1(1.4%)	0.01
Group-B ($n=35$)	2(2.9%)	8(11.4%)	13(18.6%)	9(12.9%)	3(4.3%)	Nil	Nil	

The incidence of hypoglycemia was slightly higher in Group-B (Intermittent Insulin Bolus), with 22.86% of patients affected, compared to 14.29% in Group-A (Continuous Insulin Infusion). However, this difference was not statistically significant ($p=0.38$), indicating that the mode of Insulin administration did not have a significant impact on the occurrence of hypoglycemia in this study. These findings suggest that both Insulin administration methods are relatively safe in terms of hypoglycemia risk when appropriately monitored. However, careful dosing and glucose monitoring remain essential, particularly in critically ill patients, is shown in Table-IV.

Table-IV: Frequency of Hypoglycemia Among Groups ($n=70$)

	Hypoglycemia		p -value
	Yes	No	
Group-A ($n=35$)	5(14.29%)	30(85.71%)	0.38
Group-B ($n=35$)	8(22.86%)	27(77.14%)	

DISCUSSION

Our findings demonstrate that Continuous Intravenous Insulin Infusion (CII) provides superior glycemic control with lower glucose variability and a reduced risk of hypoglycemia compared to Intermittent Insulin Bolus (IIB). Maintaining stable blood glucose levels is crucial in critically ill patients, as hyperglycemia exacerbates inflammation and immune dysfunction. CII allows for tighter glycemic control, minimizing fluctuations that could increase metabolic stress. Additionally, the lower infection rate in the CII group aligns with previous research indicating that better glucose control reduces the risk of sepsis and other complications. The shorter ICU stay in CII patients may be attributed to improved metabolic stability, potentially decreasing healthcare costs.

CII demonstrates superior glucose stability compared to IIB, which is critical in trauma and sepsis. A randomized controlled trial comparing different Insulin infusion protocols found that computerized protocols enhanced glucose control and reduced variability compared to standard methods, supporting the use of CIII for critically ill patients.¹³ Another study implementing an Insulin protocol using a multiplier-based calculation demonstrated improved glucose management in ICU patients.¹⁴ Similarly, a study evaluating graduated intravenous Insulin infusion protocols in trauma patients found improved safety and efficacy with CII.¹⁵ These findings indicate that CIII can maintain target glucose levels more effectively than IIB.

Blood glucose fluctuations can increase metabolic stress, contributing to worse patient outcomes. Research evaluating blood glucose levels before and after the implementation of an intensive Insulin infusion protocol in critically ill patients found that CII led to better glucose stabilization.¹⁶ In a pragmatic clinical trial, CII provided more stable postoperative glucose control compared to IIB in liver transplant recipients, further highlighting its benefits in maintaining glycemic stability.¹¹

CII is associated with reduced complications, including infections and organ dysfunction. A systematic review and network meta-analysis assessing Insulin infusion methods in patients receiving total parenteral nutrition found that CIII was more effective in maintaining optimal glucose control, reducing the risk of complications associated with hyperglycemia.¹⁷ The NICE-SUGAR trial also demonstrated that intensive Insulin therapy improved glycemic control but carried an increased risk of hypoglycemia, underscoring the need for protocolized Insulin titration.¹⁸ A meta-analysis further corroborated these findings, showing that CIII achieved target glucose ranges (140–180 mg/dL) more consistently than IIB, with fewer hyperglycemic episodes.¹⁹

Hypoglycemia (<70 mg/dL) remains a concern with CII but can be mitigated by standardized Insulin protocols. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes endorse nurse-driven CII protocols to balance safety and efficacy in glycemic management.¹² Additionally, the Surviving Sepsis Campaign 2021 guidelines strongly recommend CII as first-line therapy for persistent hyperglycemia (>180 mg/dL), citing improved glycemic stability and reduced organ dysfunction.²⁰ These recommendations

highlight the clinical significance of CII in managing critically ill patients.

Secondary outcomes also favor CII. A Cochrane systematic review noted that CII shortened ICU stays compared to IIB, likely due to improved glycemic stability and reduced complications.²¹ However, IIB remains viable for certain patient populations, such as those with postoperative combat injuries, where resource constraints may limit the feasibility of CII.

Emerging technologies may enhance the benefits of CII while mitigating its risks. Closed-loop (automated) Insulin delivery systems have shown promise in reducing hypoglycemia risk while maintaining tighter glycemic control compared to manual CIII. Studies evaluating closed-loop insulin delivery in critically ill patients suggest that integrating continuous glucose monitoring with automated Insulin titration can optimize glycemic management and reduce variability.²² The future of glucose control in the ICU may involve hybrid approaches that integrate AI-driven Insulin adjustments, allowing for personalized and adaptive Insulin dosing.

Despite the benefits, CIII requires intensive monitoring and skilled nursing care, making it resource intensive. The results of this 24-hour study may not directly translate to long-term clinical practice, and larger, multicenter trials are needed to validate these findings. Future studies should explore hybrid approaches, such as automated Insulin delivery systems, to optimize glycemic management in critically ill patients. Investigating the use of closed-loop Insulin delivery systems, integrating continuous glucose monitoring with AI-driven Insulin titration, or conducting multicenter randomized controlled trials could provide further insights into balancing efficacy and safety in glucose management. By leveraging technological advancements, we may refine glycemic control strategies to improve outcomes for critically ill patients.

LIMITATION OF STUDY

This study is limited by its short duration, restricting long-term outcome assessment. Single-center data may not be generalizable to broader populations. Continuous Insulin infusion requires intensive monitoring, posing feasibility challenges in resource-limited settings. Despite protocolized titration, the risk of hypoglycemia remains. Larger multicenter trials with extended follow-ups are needed to validate findings.

CONCLUSION

Continuous intravenous Insulin infusion (CIII) provides superior glycemic control, reduces glucose

variability, and lowers infection risk compared to Intermittent Insulin Bolus (IIB) in critically ill patients. CIII is associated with shorter ICU stays and improved metabolic stability. While hypoglycemia remains a concern, protocolized titration and emerging closed-loop systems enhance safety. Future research should explore hybrid Insulin delivery methods to optimize glycemic management in critical care settings.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MRI & WH: Data acquisition, data analysis, critical review, approval of the final version to be published.

FAS & AS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

TA & FM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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