Intravenous Versus Subcutaneous Insulin in Management of Hyperglycaemia in Intensive Care Unit

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ABSTRACT

Objective: To compare the efficacy and safety of intravenous Insulin infusion versus subcutaneous Insulin in the management of hyperglycaemia in intensive care.

Study Design: Quasi-experimental study.

Place and Duration of Study: Medical Intensive Care Unit of Combined Military Hospital Malir, from Jul to Sep 2021.

Methodology: 68 individuals admitted to the Medical ICU with the blood sugar levels of more than 180 mg/dl were included. Patients on one side of Intensive Care Unit were administered intravenous Insulin infusion, and on the other side were administered subcutaneous Insulin to control blood sugars. Age, gender, previous history of diabetes and use of Insulin and glycosylated haemoglobin were recorded. Efficacy of regimen was judged based on ability to achieve target glucose levels, mean blood glucose levels and total days of ICU stay. Adverse events like hypoglycaemia and hypokalaemia were recorded.

Results: Out of 68 individuals, 27 (39.70%) were administered intravenous Insulin infusion, and 41 (60.29%) were administered subcutaneous Insulin. In the intravenous Insulin group, 22 (81.5%) individuals achieved target blood glucose compared to 29 (70.7%) in the subcutaneous Insulin group. The mean blood sugars in the intravenous group were 157.11 ± 25.54 mg/dl, whereas 168.32 ± 30.49 mg/dl in the subcutaneous group (p-value=0.164). The frequency of hypoglycaemia and hypokalaemia was more in the intravenous group than in the subcutaneous group.

Conclusion: Optimal blood sugar levels were better achieved with intravenous Insulin than with subcutaneous Insulin. However, the frequency of adverse effects was also more with intravenous Insulin, so better monitoring and management are required with intravenous Insulin.

Keywords: Hypoglycaemia, Intensive care, Intravenous insulin, Subcutaneous insulin.

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INTRODUCTION

Uncontrolled hyperglycaemia in intensive care unit (ICU) settings is a common phenomenon and a significant problem encountered in intensive care patients. Maintaining optimal blood sugar levels is one of the main targets of ICU management. Both hypoglycaemia and hyperglycaemia are associated with poor outcomes, including increased mortality rates, more extended hospital and ICU stay and possibly incidence of nosocomial infections.[1] Hyperglycaemia in critical illness is usually termed Stress Hyperglycaemia. There are various proposed mechanisms of stress hyperglycaemia, but it is generally accepted that its cause is considered multi-factorial. Inflammatory mediators of sepsis and stress hormones released during a critical illness like Catecholamines and Corticosteroids are considered important causes that alter glucose metabolism. The metabolic stress associated with critical illness also leads to worsening Insulin resistance, which is associated with immune dysfunction and oxidative stress.[2] The exact definition of stress hyperglycaemia varies, but American Diabetes Association,[3] (ADA) and Society for Critical Care Medicine (SCCM) have suggested that blood sugar levels should be maintained within 140-180 mg/dl in critically ill patients.[4] Godinjak *et al*,[5] found that 54% of patients admitted to critical care had hyperglycemia on admission. Studies have also indicated that more strict glycaemic control leads to complications associated with hypoglycaemia.[6,7] Intravenous Insulin infusion has been the preferred choice of clinicians for achieving optimal glycemic control due to its rapid action.[8] However, various institutes also use basal-bolus regimens, computer-based algorithms and subcutaneous Insulin regimens. Although using these standardized regimens has resulted in lower rates of hypoglycaemia and more percentage of blood glucose readings in the optimal range, studies have not conclusively proved that they reduce mortality or ICU complications.[4] Similar efficacy of one regimen over another is also not established as all have variable advantages and disadvan-

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tages. Subcutaneous regimens have been studied rarely, so little is known about their efficacy and safety in patients in critical care. Tran *et al*,[9] studied comparison of intravenous Insulin infusion (IVII) with subcutaneous Insulin (SCI) regimen and found that IVII was associated with better glucose control. However, effectively managing an IVII was more difficult than SCI.

We conducted a study to compare IVII with SCI and study the efficacy in achieving optimal glycaemic control, side effects associated with both regimens like hypoglycaemia or hypokalaemia and management of both regimens in resource-limited settings.

METHODOLOGY

This quasi-experimental study was conducted at the Medical ICU of Combined Military Hospital (CMH) Malir, Karachi, from July to September 2021. Permission was taken from the Hospital Ethical Review Committee to conduct the study (vide letter num-ber 65/2021/Trg/ERC). The calculated sample size was 68 from the World Health Organization (WHO) sample size calculator (estimated frequency of hyperglycaemia in ICU= 54% 5, d= 0.10, and CI = 95%). Informed consent was taken from all the conscious, oriented and awake patients and from attendants of those patients who could not give consent due to critical illness.

Inclusion Criteria: All the patients admitted to Medical ICU with the age of more than 18 years and who had at least two readings of blood sugar levels >180 mg/dl were included in the study.

Exclusion Criteria: All the patients admitted and treated for diabetic ketoacidosis (DKA), or hyperosmolar hyperglycemia state (HHS) were excluded from the study.

Both sides of the ICU, having an equal number of beds (5 each), were segregated as two groups. Patients were distributed on both sides randomly, on the turn by turn basis. One side of the ICU was administered IVII, and the other side was administered SCI. Medical ICU included all types of patients with various critical illnesses like sepsis, multi-organ failure, renal and liver failure, cardiac failure and other critical patients from the medical side. Insulin was started if two consecutive readings for blood glucose were found to be more than 180 mg/dl. Patients were included in the IVII group if they received continuous variable-rate Insulin for more than 6 hours. Patients were included in the SCI group if they required a sliding scale of regular Insulin for more than two consecutive times during their ICU stay. The rate of VRII,[10] and sliding scale Insulin,[11] was calculated and adjusted as per guidelines. Patients receiving other hypoglycaemic medication or basal Insulin boluses were continued on those drugs in addition to these regimens. The previous history of diabetes and use of Insulin was recorded. Blood sugar levels were measured using the same glucometer in the ICU 4-hourly for those in the SCI group and every hour for those in IVII. Glycosylated haemoglobin (HbA1c) was measured in the main laboratory of CMH at the time of admission for all patients.

Hypoglycaemia was defined as blood sugar levels less than 70mg/dl.[12] Although the target range for blood glucose level was set to be 140-180 mg/dl, glucose levels between 71-139 mg/dl were considered harmful. Efficacy of regimen was judged based on ability to achieve target glucose levels, mean blood glucose levels and total days of ICU stay. Potassium levels were measured in the main laboratory of CMH, and hypokalaemia post Insulin therapy was defined as potassium levels less than 3.5 mmol/l in those patients with previously normal potassium levels.[13]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Descriptive statistics were applied to calculate mean and standard deviation for baseline characteristics like age, HbA1c and blood glucose levels on admission, mean blood glucose levels and the total number of ICU days. Frequencies and percentages were calculated for qualitative variables like gender, previous history of diabetes and previous use of Insulin and outcomes like episodes of hypoglycaemia and hypokalaemia and achievement of target blood glucose levels. The comparison of outcomes in two groups was made using an independent sample t-test. The *p*-value of ≤0.05 was considered significant.

RESULTS

A total of 68 individuals were included in the study, out of which 27 (39.7%) were administered IVII and 41 (60.3%) were administered SCI. There were 37 (54.4%) males and 31 (45.6%) females. Among 41 patients in the SCI group, 22 (53.7%) patients were males while 19 (46.3%) were females, almost similar percentage to the IVII group in which 15 (55.6%) were males and 12 (44.4%) were females among the total of 27 patients. The mean age was 64.07 ± 8.57 years in the SCI group and 66.00 ± 7.33 years in the IVII group. In the SCI group, 29 (70.7%) patients had a previous history of diabetes, and 14 (34.1%) patients were previously using Insulin. In the IVII group, 17 (62.3%)

patients had previous diabetes history, with 10 (37.1%) patients previously using Insulin. Mean HbA1c in the SCI group was 8.02 ± 1.32 and 8.26 ± 1.69 in the IVII group. Mean blood glucose levels on admission in the SCI group were 258.61 ± 63.35 mg/dl, while 265.48 ± 62.23 mg/dl in the IVII group (Table-I).

In the IVII group, 22 (81.5%) individuals achieved target blood glucose, while in the SCI group, 29 (70.7%) achieved optimal glycaemic control showing better results with IVII. Mean blood sugars during ICU stay in patients given IVII was 157.11 ± 25.54 mg/dl, whereas it was 168.32 ± 30.49 mg/dl in patients given SCI (*p*-value=0.164). The mean ICU stay among patients of the IVII group was 2.84 ± 1.17 days, while those administered SCI were 3.41 ± 1.78 days (*p*-value= 0.059). The frequency of hypoglycaemia in the IVII group was 5 (18.5%) compared to 5 (12.2%) in the SCI group. Similarly, the frequency of hypokalaemia was 5 (18.5%) in IVII, higher than 3 (7.3%) in the SCI group (Table-II).

Table-I: Baseline Characteristics of the Study Groups.

Baseline Characteristic		Subcutaneous Insulin n (%)	Intravenous Insulin Infusion n (%)
Gender n (%)	Male	22 (53.7%)	15 (55.6%)
	Female	19 (46.3%)	12 (44.4%)
Previous History of Diabetes n (%)	Yes	29 (70.7%)	17 (62.9%)
	No	12 (29.3%)	10 (37.1%)
Previous use of Insulin n (%)	Yes	14 (34.1%)	10 (37.1%)
	No	27 (65.9%)	17 (62.9%)
Age (Mean ± SD)		64.07 ± 8.57 years	66.00 ± 7.33 years
HbA1c (Mean ± SD)		8.02 ± 1.32	8.26 ± 1.69
Blood Sugar on Admission (Mean ± SD)		258.61 ± 63.35 mg/dL	265.48 ± 62.23 mg/dL

Table-II: Study outcomes in both groups.

Outcomes		Subcutaneous Insulin	Intravenous Insulin Infusion	*p*-value
Hypoglycemic Episode n (%)	Yes	5 (12.2%)	5 (18.5%)	
	No	36 (87.8%)	22 (81.5%)	
Hypokalemia n (%)	Yes	3 (7.3%)	5 (18.5%)	
	No	38 (92.7%)	22 (81.5%)	
Target Glucose Achieved n (%)	Yes	29 (70.7%)	22 (81.5%)	
	No	12 (29.3%)	5 (18.5%)	
Mean Blood Sugar During ICU Stay (Mean ± SD)		168.32 ± 30.49 mg/dL	157.11 ± 25.54 mg/dL	0.164
Number of ICU Days (Mean ± SD)		3.68 ± 1.79 days	2.85 ± 1.17days	0.059

DISCUSSION

Our study compared IVII with SCI for efficacy, outcomes, and safety profile. Baseline data, including mean age, male-female ratio, mean HbA1c and blood sugar levels on admission, were similar in both groups. In the study, we found that the use of IVII for managing stress hyperglycaemia in critically ill patients had better results than SCI in achieving target blood glucose levels and length of ICU stay. However, IVII treated patients had a slightly increased frequency of hypoglycaemic and hypokalaemic episodes. Mean blood glucose levels in the IVII group were 157.11 ± 25.54 mg/dl, whereas, in the SCI group, it was 168.32 ± 30.49. In a similar study by Tran *et al*,[9] the mean blood glucose was 194,[3] in the subcutaneous Insulin group and 172,[4] in the intravenous Insulin group. The difference may be due to slightly different dosing regimens and more patients in Tran *et al*,[9] study. The ove-rall reasonable control of blood sugar with IVII may be associated with frequent monitoring of blood glucose levels and timely dose adjustments. Episodes of hypo-glycaemia (18.5>12.2) and hypokalaemia (18.5 > 7.3) were more with IVII, indicating the requirement for stringent monitoring protocols to avoid complications. In a study by Dungan *et al,* the frequency of hypogly-caemia with IV Insulin was 27% vs 2.6% with SC Insulin.[14]

Although the findings may be significant, a few points need discussion. The blood glucose level at the time of admission and the initial few hours was utilized to classify stress hyperglycemia, which can miss those patients who have delayed hyperglycemia from complications related to their primary illnesses. However, it is reassuring that blood glucose concentrations within the first 24 hours are predictive of glycaemic control throughout ICU admission.[15] Similarly, the comorbid conditions leading to admission to

ICU and previous dose of Insulin already used by the patients were also not considered, which might cause the difference in the requirement of Insulin dose in individual patients.

Hyperglycaemia is a common occurrence among patients admitted to intensive care units with a critical illness (up to 80% of patients). It has been found that patients who spent greater time with higher blood glucose levels during ICU stay had higher mortality rates than those who had blood sugar levels in the optimal range.[16] Management of hyperglycaemia in ICU patients is closely linked with hypoglycaemia, which is an independent risk factor for morbidity and various complications leading to an increased rate of mortality.[17] Therefore, managing blood glucose levels is always a challenge for intensivists and clinicians managing critically ill patients. A blood sugar level in the range of 140-180 mg/dl has been recommended for ICU patients.[4,18] Another important factor is monitoring potassium levels during Insulin therapy as Insulin shifts potassium into the cells, which may cause hypokalaemia and life-threatening arrhythmias.[19] Although there is no universally accepted regimen for Insulin administration in critically ill patients, various studies have been done to compare different regimens.[20] Intravenous Insulin infusion has been a preferred option in many institutions. Short acting preparations with intermittent subcutaneous administration are also commonly used, especially in resource limited setups where continuous and strict monitoring of blood sugar levels is lacking. It is convenient and easy to understand.[21]

Although it is a well-known fact that intravenous Insulin infusions are preferable in DKA and HHS, its superiority in controlling hyperglycemia in other conditions is still under study. Our study supports the idea that intravenous Insulin is related to better outcomes in ICU settings, although it must be used with caution as it requires better monitoring.

LIMITATIONS OF STUDY

The study was done on a small scale in a single-centre. The scope of the study can be extended to critical patients admitted to surgical ICUs and multiple centres. Different centres use different dosing regimens based on clinician discretion so that result outcomes may differ in large scale studies.

CONCLUSION

The study helps in better understanding the management of hyperglycaemia in critically ill patients and its challenges. It supports preferential use of IV Insulin in ICU over SC Insulin but with caution and frequent monitoring of blood glucose and potassium levels.

Conflict of Interest: None.

Authors' Contribution

HWK: Drafting of article, acquisition of data, analysis and interpretation of data, KM: Conception of Study, study design, data collection, final approval, MIK: Analysis, interpretation of data, drafting of article, SY: Data collection, analysis and interpretation of data, AK: Data collection, analysis, MA: Data collection, analysis and interpretation of data.

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