Liraglutide as an Alternative to Insulin for Glycemic Control in Intensive Care Unit: A Randomized, Open-label, Clinical Study

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Abstract

Background: Intravenous insulin is the cornerstone in the management of hyperglycemia in the Intensive Care Unit (ICU). We studied the efficacy of liraglutide compared with insulin in the ICU. **Materials and Methods:** In this prospective, open-labeled, randomized study, we included 120 patients (15–65 years, either sex) admitted to ICU with capillary blood glucose (CBG) between 181 and 300 mg/dl. We excluded patients with secondary diabetes and APACHE score >24. The patients were divided into two groups ($n = 60$) based on the CBG: Group 1 (181–240) and Group 2 (241–300). They were randomized further into four subgroups ($n = 30$) to receive insulin (Groups 1A and 2A), liraglutide (Group 1B), and insulin with liraglutide (Group 2B). The primary outcome was the ability to achieve CBG below 180 mg/dL at the end of 24 h. The secondary outcomes include mortality at 1 month and hospital stay. Data and results were analyzed using Mann-Whitney U-test, paired t-test, and Chi-square tests. **Results:** The mean age of the patients (93M and 27F) was 57.1 ± 13.9 years, hospital stay (16.9 ± 7.5 days), and CBG was 240.5 ± 36.2 mg/dl. The primary outcome was reached in 26, 27, 25, and 28 patients of Groups 1A, 2A, 1B, and 2B, respectively. The 30-day mortality and hospital stay were similar across all the four groups. Hypoglycemia was common with insulin and gastrointestinal side effects were more common with liraglutide ($P < 0.001$). **Conclusion:** Liraglutide is a viable alternative to insulin for glycemic control in the ICU. Further studies with a larger number of patients are required to confirm our findings.

Keywords: Critical care, hyperglycemia, insulin, Intensive Care Unit, liraglutide

INTRODUCTION

Hyperglycemia is frequently observed metabolic abnormality in a critical care setting. Observational studies have shown that admission hyperglycemia is associated with higher mortality and morbidity.[1] The stress hyperglycemia was considered to be a beneficial response previously, to provide excess fuel to the tissues.[2] However, the concepts of hyperglycemia in the Intensive Care Units (ICUs) were revolutionized by Leuwen *et al.*, who showed beneficial effects of intensive glucose control in a group of patients admitted to surgical ICU.[3] Subsequent studies from the same group and others did not show a similar trend, which generated a lot of debate in the past decade.[4] The debate was laid to rest by NICE-SUGAR study and the majority of the researchers now agree that good glycemic control is beneficial and intensive control may be useful in only select situations.[5,6] The controversy over the management of hyperglycemia in ICU extends beyond hyperglycemia into selecting the ideal therapeutic option.[7] Insulin remains the cornerstone in the management of critically ill patients. However, hypoglycemia remains a major limiting factor for the intensive insulin therapy and is an independent predictor of mortality.[8]

During the past decade, several new drugs have been approved for the management of type 2 diabetes mellitus (T2DM). A few of them have revolutionized the management of T2DM and its complications. Incretin modulators are a group of antidiabetic drugs which increase the endogenous glucagon-like peptide-1 (GLP-1) levels.[9] They include the GLP-1 analogs (liraglutide and exenatide) and enhancers (gliptins). Liraglutide is a long-acting GLP-1 analog used in T2DM and has even shown to be beneficial in preventing cardiovascular deaths.[10] Incretin modulators have been shown to be beneficial in ICU settings due to their low risk of hypoglycemia, reduction of

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inflammation, and blood pressure.[11] The specific beneficial actions of liraglutide in ICU include the amelioration of stress-induced hyperglycemia by reducing glucagon and increasing insulin secretion.[12] Extensive literature search did not reveal any studies exploring the benefits of liraglutide in ICU from India. Hence, we conducted this study to compare the efficacy and safety of the use of liraglutide with insulin in the management of hyperglycemia in critically ill.

MATERIALS AND METHODS

Study population

We conducted this randomized, prospective, open-label study at a tertiary level referral hospital of the armed forces located in Delhi. All patients admitted to the ICU (either sex, aged between 15 and 65 years) with an admission capillary blood glucose (CBG) value between 181 and 300 mg/dL were included in the study. We excluded patients with intake of drugs that could affect the glycemic status (glucocorticoids and octreotide). We excluded patients with known contraindications to the liraglutide (hypersensitivity, pancreatitis, creatinine clearance <30 ml/min, pregnancy and lactation, diabetic ketoacidosis and hyperosmolar hyperglycemic state, gastroparesis, malignancy, type 1 diabetes mellitus, secondary diabetes mellitus, and APACHE II Score >24). We excluded sick patients because the efficacy of liraglutide was not evaluated earlier in such patients and also for the significant risk of gastrointestinal side effects with the use of liraglutide. We also excluded patients who had a significant systemic ailment with an elevated risk of hypoglycemia such as end-stage renal disease, fulminant hepatic failure, and terminal care oncologic patients. The local Ethics Committee approved the trial protocol and the written informed consent was obtained from either the patients or their authorized attendants. The flow diagram of the study is given in Figure 1.
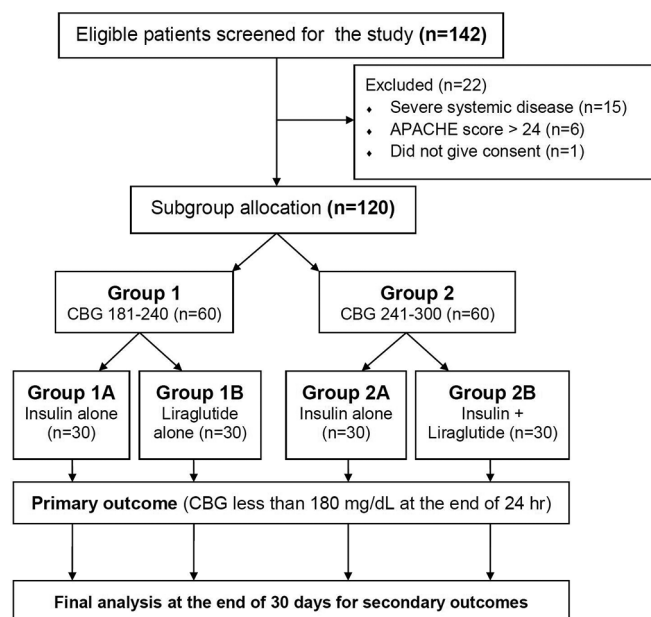

Figure 1: Flow diagram of the study

Study measures

A detailed history regarding the history of diabetes and its complications was obtained from all the participants. The patients were initially divided into Groups 1 and 2 based on the admission CBG. Patients in each group were further randomized using the computer-generated random number sequencing into subgroups A and B as shown in Figure 1. The patients were managed in the ICU by the in-charge doctors in consultation with the critical care team. The treating team was not aware of the subgroup of the patient and would always request for a better glycemic control as per the existing guidelines on the subject. Any clinical deterioration and worsening of APACHE score >24 trigger an alarm and insulin therapy. The clinical and biochemical assessment was done every day for 3 days and weekly for 1 month. The treating team adjudicated the relation between dysglycemia and the cause of mortality in every deceased patient. The primary outcome was the CBG <180 mg/dL at the end of 24 h stay in ICU. The secondary outcomes include mortality at the end of 1 month, duration of hospital stay, and the glycemic variability calculated as the coefficient of variance (CoV). We also analyzed the adverse events to the therapy including the rate of hypoglycemia between the four groups.

Study intervention

After the randomization into any of the four groups, the patients were treated with either insulin or liraglutide. Liraglutide was administered as a subcutaneous injection in a daily fixed dose of 1.2 mg for all the patients. The details about the insulin initiation and dose adjustment are given in the supplementary appendix. The glycemic monitoring was done hourly by CBG in all the patients for 24 h. Subsequent monitoring has been done as per the glycemic level and the prevailing clinical condition. All the previous oral hypoglycemic agents (OHAs) were withdrawn in the patients. The OHAs were given after the initial 72 h depending on the primary condition of the patient. The rescue therapy with insulin was given to patients in Group 1A if they fail to achieve the target CBG within 24 h. All the measurements of the CBG were done using the One Touch Select Simple Glucometer manufactured by the Lifescan, Inc., Johnson and Johnson®, California, USA.

Study definitions

T2DM was diagnosed based on the self-reporting or using the ADA guidelines.[13] Stress hyperglycemia was diagnosed in patients with admission CBG >180 and glycosylated hemoglobin (HbA1c) <6.5% without a history of T2DM. Hypoglycemia was defined as CBG <70 mg/dL as suggested by the ADA guidelines. The glycemic target was decided below 180 mg/dL, as per the recent guidelines on the management of hyperglycemia in critically ill.[14]

Statistical analysis

Data are presented as mean ± standard deviation and a comparison between the groups was done using Mann–Whitney U-test and paired *t*-tests. The categorical variables are

presented in frequencies along with respective percentages and were compared using Chi-square test. The data analysis was done using the intention to treat principle and a *P* < 0.05 was considered statistically significant in all the tests.

RESULTS

A total of 120 patients (93 Males and 27 Females) were included in the study. The mean age of the patients was 57.1 ± 13.9 years, hospital stay (16.9 ± 7.5 days), HbA1c at admission (7.3 ± 1.6%), CBG at admission (240.5 ± 36.2 mg/dl), and mean APACHE score was 10.1 ± 2.2. A total of 46 (38.3%) patients had a past history of T2DM and another 53 (44.16%) patients were diagnosed to have stress hyperglycemia. The clinical diagnoses of the patients admitted to ICU were given in Table 1. The patients with cardiovascular disorders are admitted to CCU and are not included in this study. The comparison of the baseline parameters between the four groups and the clinical outcomes is given in Table 2. In brief, the primary outcome was achieved in a significant number of patients (*n* = 106) across all the groups (*P* > 0.05). Only 14 patients did not achieve the target CBG and were spread equally across all the groups. A total of five patients

Table 1: Baseline diagnosis of study participants

Diagnosis	*n* (%) (total *n*=120)
Neurological disorders	24 (20)
Infectious diseases	20 (16.6)
Gastrointestinal disorders	19 (15.8)
Postsurgical monitoring	19 (15.8)
Oncological disorders	11 (9.2)
Electrolyte abnormalities	11 (9.2)
Kidney disorders	7 (5.8)
Poisoning	4 (3.3)
Miscellaneous	5 (4.2)

(3 failure and 2 drug intolerance) in Group 1B had to be given rescue insulin therapy.

A total of seven deaths occurred during the observation period with no significant difference between the groups. None of the deaths were found attributable to dysglycemia by the treating team. The mean CoV in the entire study population was 0.22 ± 0.06, and the distribution across the groups is shown in Table 1. The CoV was relatively high in patients using insulin when compared with the liraglutide. The duration of hospital stay did not differ with the antihyperglycemic agent and admission CBG. There was a significantly greater incidence of nausea in patients using the liraglutide as compared to insulin group. There were a total of 38 episodes of hypoglycemia (CBG <70 mg/dL) during the entire study period, and the incidence was more in patients using insulin. The mean time to achieve glycemic control was 9.9 ± 5.9 h, which was higher in Group 2 as expected. In the combined analysis, the patients treated with insulin (Group 1A and 2A) achieved glycemic control earlier than the liraglutide (*P* = 0.0356).

DISCUSSION

Our study showed that the use of liraglutide in ICU could achieve a comparable glycemic control to insulin. Marso *et al*. have shown excellent results with the use of a short-acting GLP-1 analog (Exenatide) in critically ill cardiac ICU patients.[15] The use of GLP-1 analogs has also reduced the need for the bolus therapy in the traditional basal-bolus regimen of the insulin.[16] Liraglutide is being studied in a multicenter trial for the control of perioperative hyperglycemia and has recently been shown to prevent the cardiovascular mortality in T2DM.[10,17] A recent report showed similar benefit using sitagliptin (Incretin enhancer) along with basal insulin.[18] The benefits of liraglutide in

Table 2: Comparison of baseline parameters and outcomes in all four groups

Parameter	Units	Group 1A (*n*=30)	Group 1B (*n*=30)	*P*	Group 2A (*n*=30)	Group 2B (*n*=30)	*P*
Age	Years	55.1±13.1*	58.9±12.7	0.2587	55.5±17.1	58.8±12.5	0.3970
Sex	Male:female	24:6	22:8	0.7611	24:6	23:7	1.0000
History of DM	Yes:no	14:16	12:18	0.7948	10:20	10:20	1.0000
Height	cm	167.3 (7.7)	168.3 (6.6)	0.5912	168.7 (6.8)	167 (7.8)	0.3719
Body weight	kg	87.8 (17.1)	86.7 (16.5)	0.8007	80 (17.5)	86.1 (19.6)	0.2086
Body mass index	kg/m²	31.5 (6.7)	30.8 (6.4)	0.6805	28.9 (6.9)	31.1 (7.9)	0.2554
HbA1c	%	6.8 (1.4)	6.8 (1.5)	1.0000	7 (1.5)	7.6 (1.7)	0.1526
CBG at admission	mg/dL	209 (19.7)	211.2 (18)	0.6533	269.3 (18.8)	274.3 (15.8)	0.2694
CBG at 24 h	mg/dL	143.4 (12.2)	137.8 (15.6)	0.1269	148.6 (22.4)	151.2 (19.7)	0.6349
Primary outcome	*n*	26	27	1.0000	25	28	0.4238
CoV of glucose	*n*	0.21 (0.05)	0.17 (0.04)	0.0011	0.25 (0.06)	0.23 (0.03)	0.1079
Mortality at 30 days	*n*	2	1	1.0000	2	2	1.0000
Hospital stay	Days	16.7 (7.2)	15.9 (9.2)	0.7090	19.3 (8.5)	16 (7.1)	0.1081
Nausea/vomiting	*n*	2	9	0.0419	3	10	0.0575
Hypoglycemia	*n*	10	3	0.0575	18	7	0.0082
Time to glucose control	h	6.1 (4.5)	6.8 (2.5)	0.4594	11.6 (4.9)	16.3 (4.2)	0.0002

*Mean±SD. DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin; CBG: Capillary blood glucose; CoV: Coefficient of variance; SD: Standard deviation

critical care settings extend beyond the obvious glycemic control. Stress hyperglycemia in critical illness is due to the release of many counterregulatory hormones (cortisol, catecholamines, glucagon, and growth hormone) that increase the peripheral insulin resistance.[19] Liraglutide specifically counters this mechanism by inhibiting the release of glucagon and reduces hyperglycemia. Stress-induced hyperglycemia predicts the progression to T2DM and is observed in almost half of our patients.[20] Our hospital, being a tertiary level referral center for the armed forces, receives mostly male patients. This explains the gender bias and male predominance in our study.

In our study, only 46 patients were known diabetics, whereas the remaining 74 did not have a diagnosis of DM. Umpierezz *et al.* showed the presence of hyperglycemia in 38% of admitted patients, of whom only 26% with a past history of T2DM.[21] The observed variation in the ratio in our study could be explained by the different demography and the referral bias of our hospital. A total of seven deaths occurred during the study period which was not different with respect to the underlying therapy. The lesser mortality in our study could be due to the exclusion of patients with severe organ failure, relatively younger age group, and a lower APACHE score at baseline. Previous trials have shown no difference in mortality in GLP-1 analog treatment in comparison to insulin.[22] In fact, the addition of liraglutide to standard care has shown to reduce the cardiovascular mortality and morbidity in T2DM.[10]

The time to achieve a steady state of glucose control varies between insulin and liraglutide due to the differences in their mode of action, pharmacokinetics, and pharmacodynamics. Abuannadi *et al.* showed that the time to achieve glycemic control in critically ill patients was 12 h (Range 5 and 24 h) when moderate intensity insulin treatment was given.[23] A previous report using the intravenous exenatide infusion has shown the time to glycemic control within 150 min.[15] However, we used the subcutaneous injection precluding any direct comparison with another study. The use of liraglutide has shown to produce less glycemic variability as reported in other studies albeit in non-ICU setting.[24] In our study, a higher number of patients receiving liraglutide had reported with nausea and vomiting. This could have been minimized with initial dose of 0.6 mg, but our protocol did not allow the same. There is a higher incidence of hypoglycemia in the insulin-treated group than the liraglutide-treated group as expected. The strengths of our study include the seminal nature of the study, robust follow-up in a single center, and randomized design of the evaluation. The limitations of our study include small sample size, use of CBG instead of the continuous glucose monitoring, failure to titrate the dose of the liraglutide, and use of an indirect measure such as CoV for estimation of the glucose variability. Another limitation is the exclusion of critically ill (APACHE score >24) patients, in whom the outcomes would have differed with the use of liraglutide instead of insulin.

Conclusion

Our study provides an initial evidence to support the use of liraglutide for the treatment of hyperglycemia in ICU with comparable efficacy to that of insulin. Liraglutide has been associated with less glycemic variability, higher gastrointestinal side effects, and similar mortality rates with that of insulin. Further large-scale studies with more number of patients would confirm the findings observed in our study.

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Conflicts of interest
There are no conflicts of interest.

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