ORIGINAL ARTICLE

Insulin Degludec vs Insulin Glargine for Glycemic Control in Critical Illness Hyperglycemia

Ibrahim Mohammed El Sherif[1], Adham Magdy Haggag[2], Mohamed Hussen Abbas[3], Walid Y Kamel[4]

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Abstract

Aim and background: Hyperglycemia is a serious condition and associated with an increased risk of complications and mortality in both critically ill and non-critically ill people. Improvement in the glycemic level reduces the length of hospital stay, systemic infections and short- and long-term mortality. The aim was to test the effectiveness of insulin degludec vs insulin glargine and regular insulin in controlling blood sugar in patients with critical hyperglycemia.

Materials and methods: Using random control trial, the patients were randomly divided into three equal groups—group R, group G and group D. Each group included 30 patients. Group G was managed using regular insulin together with an insulin glargine. Group D was managed using regular insulin together with an insulin degludec. However, group R was managed using only regular insulin.

Results: The incidence of hypoglycemia was statistically more significant in the group of regular insulin than in groups G and group D with a *p*-value 0.0069. There was no statistically significant difference between the three groups regarding the frequency of hypoglycemia.

Conclusion: Ultra-long-acting insulin can effectively control random blood sugar (RBS) with a decrease in the total dose of insulin used. It is recommended that using insulin degludec is a safe and effective alternative to regular insulin for glycemic control in critically ill patients.

Keywords: Critical patients, Glargine, Hyperglycemia, Insulin degludec, Stress.

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Highlights

Hyperglycemia is a major risk factor for increased postoperative morbidity and mortality. The effectiveness of insulin degludec vs insulin glargine in the control of blood sugar in critical illness hyperglycemia. Ultra-long-acting insulin can effectively control the random blood sugar (RBS) with a decrease in the total dose of insulin used.

Introduction

Stress hyperglycemia, or critical illness hyperglycemia, is common in critically ill patients. In this population, hypoglycemia is also associated with poor outcomes, including a higher mortality rate, increased length of stay in the intensive care unit (ICU) stays, and an increased incidence of nosocomial infection, which have raised the efforts towards optimal glycemic control.[1,2]

The hypothalamic adrenal axis, sympathoadrenal system and some of the proinflammatory cytokines (TNF-α, IL-1 and IL-6) act in synergism to induce stress hyperglycemia.[3] Insulin resistance may be a contributing factor.[4] The main etiologies for hypoglycemia in critically ill patients are insulin administration, sepsis, and abrupt changes in parenteral nutrition.

High incidence of hypoglycemia with short-acting Insulin, the drug of choice in the management of hyperglycemia in hospitalized patients, especially hemodynamically unstable patients, those critically ill patients treated with intensive insulin therapy. Those who are hemodynamically stable with persistent hyperglycemia could be effectively controlled with long-acting agents such as insulin glargine to ensure a stable serum glucose profile with a twice/day dose rather than once per day.[5,6]

The first edition of long-acting basal insulin analogues, Insulin glargine, compared to neutral protamine Hagedorn (NPH) insulins, was found to reduce the incidence of nocturnal hypoglycemia, while having an estimated duration of action ranging from 18 to 25 hours.[4] Insulin degludec's lengthy duration of action is attributed to the persistent release of the separated monomers from the soluble polyhexamer at the injection site, resulting in stable pharmacokinetic profiles under steady-state conditions.[7]

Insulin degludec's steady pharmacokinetic profile lowers the risk of hypoglycemia, as well as morbidity and mortality.[8,9] Given this, there is compelling physiological and clinical evidence to suggest the potential advantages of insulin degludec, which may help to lower insulin dose due to its prolonged duration of effect.

Aims of the Study

The aim was to test the effectiveness of insulin degludec in comparison to insulin Glargine and regular insulin in controlling blood sugar levels in critical illness hyperglycemia.

[1,2,4]Department of Anaesthesia, ICU and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[3]Department of Internal Medicine, National Research Centre, Dokki, Egypt

Corresponding Author: Ibrahim Mohammed El Sherif, Department of Anaesthesia, ICU and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt, Phone: +01092286819, e-mail: dribrahim.elsayed@med.asu.edu.eg

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Conflict of interest: None

Table 1: The sliding scale short/rapid-acting insulin dose

	AC			
BG mg/dL	*Highly insulin sensitive (total daily doses <0.5 U/kg/day)*	*Normal insulin sensitivity (most patients) (total daily doses 0.5–1 U/kg/day)*	*Highly insulin resistant (total daily doses >1 U/kg/day)*	*HS*
<150	0 U	0 U	0 U	
150–199	1 U	2 U	3 U	
200–249	2 U	4 U	6 U	
250–299	3 U	6 U	9 U	0–2
300–349	4 U	8 U	12 U	2–4
≥350	5 U	10 U	15 U	4–6

Materials and Methods

Study Population

The study was carried on the patients admitted to the general ICU at Ain Shams medical intensive care over a period of 6 months.

Ethical Approval and Clinical Trial Registration

After informed consent and the approval of the research ethics committee of the faculty of medicine at Ain Shams University, with approval number FAMSU R322/2023. This study is a randomized controlled clinical trial with a clinical trial registry number of NCT06178874.

Sample Size and Study Groups

Using the PASS 15 program for sample size calculation, reviewing results from the previous study (Fatati et al., 2018) showed that IDeg in hospitalized patients with or without T2DM who require nutritional support has the potential to maintain a stable level of BG and reduce glycemic variability. Assuming an effect size difference of 0.8 between the two groups regarding RBS level and after 10% adjustment for dropout rate, a sample size 30 patients per group achieves 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.8 and the significance level (alpha) is 0.050 using a two-sided two-sample equal-variance *t*-test. The patients were randomly divided into three equal groups; group R, group G and group D, Randomization was done by computer-generated number lists.

Inclusion Criteria

- Patients between the ages of 18 and 60.
- Elevated blood sugar that remains above 250 mg/dL for over 24 hours.

Exclusion Criteria

- Patients below the age of 18.
- Elderly patients who are over 60 years old.
- Ketoacidosis in patients with diabetes.
- Patients experiencing repeated incidents of hypoglycemia.
- Patients declined to take part in the research.
- Patients suffering from renal impairment.
- Patients receiving corticosteroids.

Study Outcomes

The primary outcome was to study the effect of long-acting insulin (insulin degludec) in controlling the RBS in included patients.

The secondary outcome was to study the impact of using long-acting insulin with a long-acting duration of action on the duration of ICU stay.

Study Procedures

All Patients were Subjected to the Following:

Monitoring with the standard monitor as per the protocol of the unit including devices such as pulse oximeter, electrocardiogram, and non-invasive blood pressure monitoring. The data were settled to record every 15 minutes.

In Group R

The blood sugar level was controlled using regular insulin only by the regimen as shown in Table 1.

In Group G

Insulin Glargine was added at a dose of 0.2 units/kg, given SC, at 9 PM and the dose was titrated to reach the target blood level control.

In Group D

Insulin degludec was added initially at a dose of 0.2 units/kg given by SC route and was titrated based on the clinical situation and was administered at 9 PM.

The following data were monitored and collected, the total dose of insulin used, the hypoglycemic events (hypoglycemia was defined as a reduction of blood sugar less below 60 gm/dL), the duration of stay in the critical care unit, the potassium level in serum, and the incidence of mishaps limited to diabetic ketoacidosis and acute kidney injuries or risk. The acute kidney risk/injuries were diagnosed by:

Reduction of urinary output less than 0.5 mL/kg/h for more than 6 hours and/or a 1.5–2 times baseline elevation of serum creatinine.

Reduction of urinary output less than 0.5 mL/kg/h for more than 12 hours. and/or a 2–3 times baseline elevation of serum creatinine in case of acute kidney injuries.

Complete blood count, liver enzymes, renal function tests, serum creatinine, serum K^+ and Na^+ levels, serum level of albumin and RBS were measured at admission and then every 3 days thereafter, unless there was a need for closer monitoring. Glycated hemoglobin was obtained once.

Using a glucometer (Accu check active), blood sugar levels were measured every hour, and any changes were recorded.

Action for Hypoglycemia

Mild (Adults Who are Conscious, Orientated and Able to Swallow)

Checked ABCDE, discontinue IV insulin, and provide 15–20 gm of quick-acting carbohydrate by 5–7 sugar canned pills or 150–200 mL of pure fruit juice. After 10–15 minutes, the blood glucose level was measured, and if it remained below 70 mg/dL, the

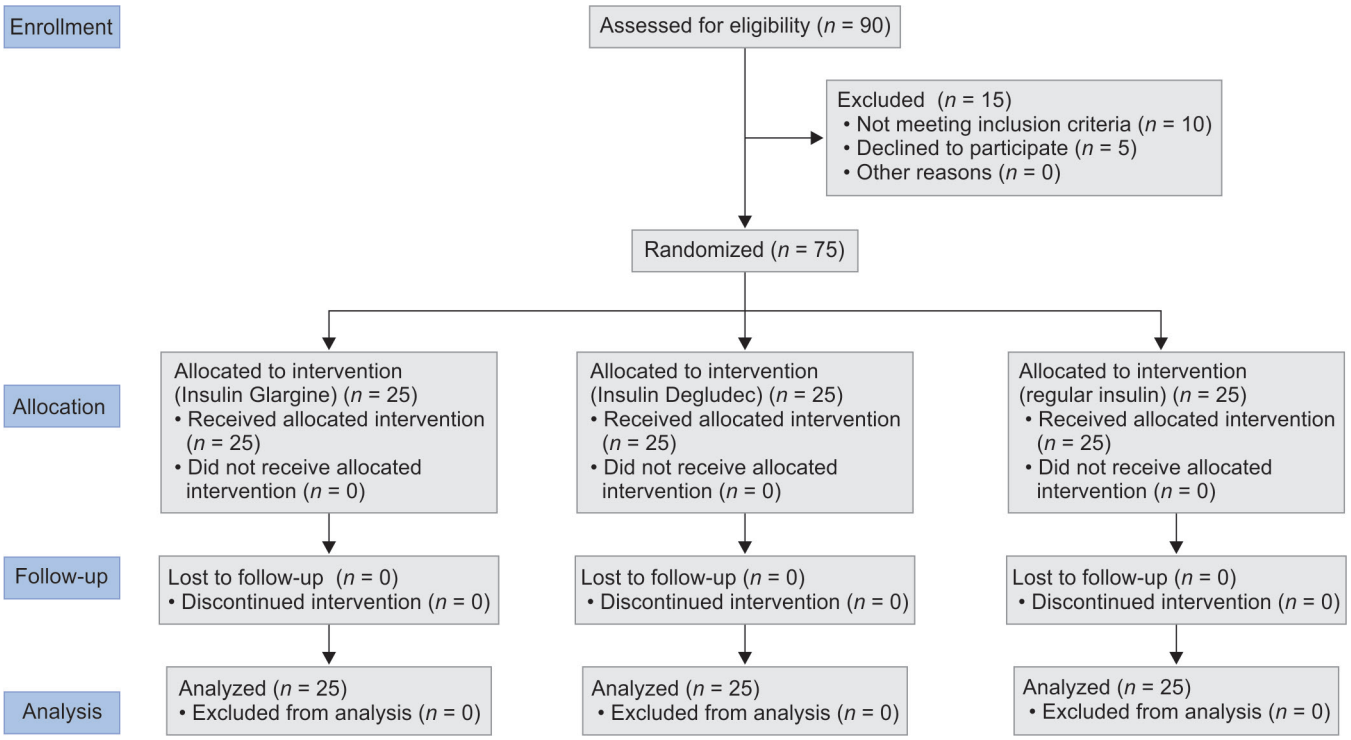

Fig. 1: A consolidated standards of reporting trials diagram

preceding therapy was repeated up to three times. If there was no response, 20 mL of 20% IV dextrose was administered.

Moderate (Confused, Disorientated, or Agitated)

Checked ABCDE, IV insulin was stopped. If the patient was capable and cooperative, they were treated for mild hypoglycemia. If they were uncooperative but could swallow, 2 tubes of 40% glucose gel were squeezed into mouth. After 10–15 minutes, the blood glucose level was checked, and if it was persistently less than 70 mg/dL, the procedure was repeated three times.

Severe (Unconscious, Agitated or Nil by Mouth)

Checked ABCDE, discontinue IV insulin. Over a period of 15 minutes, provide 100 mL of 20% dextrose. After 10 minutes, the random blood glucose level was measured; if it was less than 70 mg/dL, the regimen was treated as above.

For All Degrees of Hypoglycemia

All groups will restart IV regular insulin at a rate of 0.5 U/hour after glucose levels surpass 70 mg/dL. Groups G and D will also have a 20–30% decrease in their subsequent subcutaneous long-acting insulin dosage.

Statistical Analysis

Data were collected, coded, tabulated, and then analyzed using the SPSS software package (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., 2013). Central tendencies for numerical variables was presented as mean (standard deviation) or median (Q1–Q3), when appropriate, and frequency table were used for categorical variables. Comparisons of numerical variables by using one-way ANOVA or Kruskal–Wallis test as appropriate, while Chi-square tests were used for comparisons of nominal variables. Kaplan–Meier survival analysis with a long-rank test was used to compare time to achieve the target. Pairwise comparisons were done when indicated. Any difference with a p-value < 0.05 is considered statistically significant.

Results

A consolidated standards of reporting trials diagram (Fig. 1) showed that 90 patients were assessed for eligibility to participate in the study, 15 of which were excluded either for not meeting the inclusion criteria or for refusal to participate. The remaining 75 patients were allocated equally to the three study groups and received the assigned type of insulin. All the randomized patients completed the study and were analyzed in the study results.

There was no statistically significant difference between the three groups (regular insulin, degludec insulin, glargine insulin) with regard to age, APACHE score, RBS on admission, ICU length stay, hospital stay, serum creatinine, serum cholesterol, HbA1c, serum potassium, average plasma glucose, and time to control, as in Tables 2 and 3.

According to Kaplan–Meier survival analysis, the patients in the three groups reached the target plasma glucose levels in a comparable amount of time with no statistically significant difference (Fig. 2). However, group R needed significantly more insulin units overall to reach the target level, as shown in Tables 4 and 5.

A one-way ANOVA was conducted to determine if the total dose of insulin given was different for the three groups. The data is presented as mean ± standard deviation. The insulin dose was statistically significantly different between the 3 groups, $F(2, 72) = 309.016$, $p < 0.001$. It is highest in the insulin group (122.32 ± 28.6) compared to both the glargine and the degludec (18.52 ± 6.2) and (17.68 ± 4.5) respectively. *Post hoc* analysis with a Bonferroni adjustment was used for multiple comparisons. A Bonferroni correction was made, with statistical significance accepted at a p-value < 0.0167. Pairwise comparisons revealed that the insulin

Table 2: Patient characteristics on admission, ICU stay length, hospital stay length, average plasma glucose on stay, and time to control

Data during ICU stay	*N*	*Mean*	*Std. Deviation*	*95% Confidence interval for mean*		*p-value*
				Lower bound	*Upper bound*	
Age (Year)						
Group R	25	49.80	8.317	46.37	53.23	
Group D	25	53.00	6.062	50.50	55.50	0.199
Group G	25	53.00	7.006	50.11	55.89	
APACH score						
Group R	25	12.04	2.806	10.88	13.20	
Group D	25	11.96	2.226	11.04	12.88	0.975
Group G	25	12.12	2.505	11.09	13.15	
RBS on admission (mg/dL)						
Group R	25	352.48	67.657	324.55	380.41	
Group D	25	310.44	53.872	288.20	332.68	0.057
Group G	25	328.72	60.603	303.70	353.74	
Days of ICU stay (day)						
Group R	25	7.92	1.891	7.14	8.70	
Group D	25	7.80	1.893	7.02	8.58	0.378
Group G	25	7.24	1.690	6.54	7.94	
Serum creatinine (mg/dL)						
Group R	25	0.964	0.2215	0.873	1.055	
Group D	25	0.920	0.2082	0.834	1.006	0.576
Group G	25	0.984	0.2285	0.890	1.078	
Serum cholesterol (mg/dL)						
Group R	25	184.32	33.615	170.44	198.20	
Group D	25	177.82	24.127	167.86	187.78	0.704
Group G	25	182.40	25.698	171.79	193.00	
HbA1C (%)						
Group R	25	8.808	1.2176	8.305	9.311	
Group D	25	8.756	1.1962	8.262	9.250	0.981
Group G	25	8.740	1.4110	8.158	9.322	
Serum potassium (mmoL/L)						
Group R	25	4.044	0.4350	3.864	4.224	
Group D	25	4.152	0.4214	3.978	4.326	0.535
Group G	25	4.048	0.2815	3.932	4.164	
Hospital stay (day)						
Group R	25	12.20	4.163	10.48	13.92	
Group D	25	10.68	2.780	9.53	11.83	0.268
Group G	25	11.56	2.740	10.43	12.69	
Average plasma glucose (mg/dL)						
Group R	25	175.57	18.775	167.82	183.32	
Group D	25	181.37	13.938	175.61	187.12	0.394
Group G	25	176.37	15.393	170.02	182.72	
Time to control (day)						
Group R	25	2.76	2.127	1.88	3.64	
Group D	25	3.28	1.400	2.70	3.86	0.609
Group G	25	3.16	2.154	2.27	4.05	

One way ANOVA

dose given in the insulin group is statistically significantly higher than both the glargine group ($p < 0.001$) and the degludec group ($p < 0.001$), but no other group differences were statistically significant, as shown in Table 6.

The incidence of hypoglycemia was statistically significant in the group given regular insulin in comparison to group G and group D as in Table 7. There was no statistically relevant difference among the three groups regarding the frequency of hypoglycemia as in Tables 8 and 9.

Discussion

Hyperglycemia is associated with higher postoperative morbidity and mortality. Glargine insulin improves short as well as longterm

Table 3: The gender among the patients population

	Group			
Gender	*Group R*	*Group D*	*Group G*	*p-value**
Female				
Count	6	7	6	
% within group	24.0%	28.0%	24.0%	
Male				
Count		18	19	0.932
% within group	76.0%	72.0%	76.0%	
Total				
Count	25	25	25	
% within group	100.0%	100.0%	100.0%	

*Chi-square tests

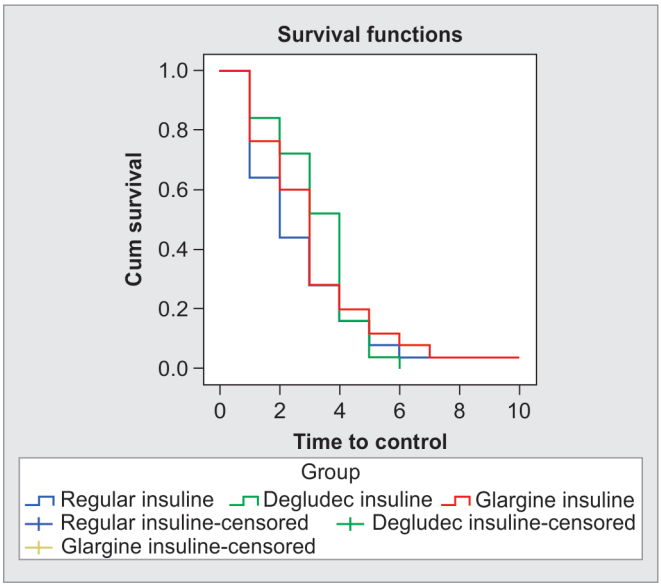

Fig. 2: Time to achieve the target serum glucose level among the three groups

Table 4: Patients achieved target plasma glucose levels

	Group			
Achieve target levels	*Regular insulin*	*Degludec insulin*	*Glargine insulin*	*p-value*
No				
Count	1	0	1	
% within group	4.0%	0.0%	4.0%	
Yes				
Count	24	25	24	0.598
% within group	96.0%	100.0%	96.0%	
Total				
Count	25	25	25	
% within group	100.0%	100.0%	100.0%	

One-way ANOVA

survival. It is expected that glargine insulin administration as basal insulin once a day causes proper control in the blood glucose level without causing hypoglycemia.[10] Combination of

Table 5: Total dose of insulin among the three groups

	Group			
Total dose of insulin in mg/dL	*Group R*	*Group D*	*Group G*	*p-value*
Mean	41	17.68	18.52	
STD	28.6	4.52	6.29	
Min.	63	12	13	
Max.	174	45	34	0.0001*
Total				
Count	25	25	25	
% within group	100.0%	100.0%	100.0%	

*One-way ANOVA

glargine with continuous insulin infusion in patients scheduled for revascularization surgery will prevent blood glucose levels fluctuation and provides better glycemic control.[11]

For critically ill patients, glycemic control can be safely and effectively achieved with the use of insulin glargine instead of regular insulin. The efficacy of glargine against regular insulin in regulating the random blood glucose (RBS) level was studied by Bhattacharyya et al. Except the glargine arm, where the RBG at 0 was 10.0 mmoL/L while it was at 6 hours about 9.9 mmoL/L, compared to 9.4 mmoL/L and 8.3 mmoL/L in group R, with a *p*-value = 0.04 and 0.02, the median RBGs at 6-hour were comparable in both groups. But according to Bhattacharyya et al. study findings, group G experienced three hypoglycemic episodes, whereas group R experienced only one.[12]

The current study reported the effectiveness of the three studied groups in achieving the target serum level with no statistical difference, moreover the episodes of hypoglycemia were higher in control group R than in group G or group D.

Our findings concurred with those of a study by Nader et al. that examined the impact of longer-acting insulin on lowering blood-glucose fluctuations in an ICU and came to the conclusion that insulin glargine is a more effective way to lower blood glucose levels and lessen hyperglycemic episodes than regular insulin use. They hypothesized that this may result in fewer ICU stays or more hypoglycemia episodes.

In contrast to our research, Nader et al. found that the glargine group's average daily blood glucose level was considerably lower than the controls' ($p < 0.0001$). The glargine group experienced a higher frequency of hypoglycemia and a 2-day shorter length of stay in the ICU.[13] Although there was no difference in the frequency of hypoglycemia in our trial, group R experienced a much greater incidence of hypoglycemia than either group G or group D, with no difference in the length of intensive care stay.

The increase in the incidence of hypoglycemia in the current study could be explained by Stapleton et al., who stated in their 2023 study that due to varying definitions of hypoglycemia among critical ill patients, the reported incidence of hypoglycemia varies among studies between 19% when defined as blood glucose level of less than 40 mg/dL to as high as 32% when blood glucose level of less than 60 mg/dL was used to define hypoglycemia.[14–16]

According to the current study, the adding of insulin glargine and insulin degludec could decrease the total dose of insulin used to safely reach the target plasma level with a stable profile as revealed by lower or no episodes of hypoglycemia.

Oya et al. as well as Heise et al. have derived to the same conclusion on studying the outcomes of insulin degludec and

Table 6: *Post hoc* analysis for multiple comparison for the three groups

					95% Confidence interval	
(I) Group	*(J) Group*	*Mean difference (I–J)*	*Std. error*	*Sig.*	*Lower bound*	*Upper bound*
insulin	Glargine	103.800*	4.841	0.000	91.93	115.67
	Degludec	104.640*	4.841	0.000	92.77	116.51
Glargine	Insulin	–103.800*	4.841	0.000	–115.67	–91.93
	Degludec	0.840	4.841	1.000	–11.03	12.71
Degludec	Insulin	–104.640*	4.841	0.000	–116.51	–92.77
	Glargine	–0.840	4.841	1.000	–12.71	11.03

*Bonferroni test

Table 7: Hypoglycemia incidence

	Group			
Hypoglycemia	*Regular insulin*	*Degludec insulin*	*Glargine insulin*	*p-value*
No				
Count	15	25	22	
% within group	60.0%	100.0%	88.0%	
Yes				
Count	10	0	3	0.0069*
% within group	40.0%	0.0%	12.0%	
Total				
Count	25	25	25	
% within group	100.0%	100.0%	100.0%	

*Fisher exact test

Table 8: Frequency of hypoglycemia

	Group			
Frequency of hypoglycemia	*Regular insulin*	*Degludec insulin*	*Glargine insulin*	*p-value**
No				
Count	22	25	22	
% within group	88.0%	100.0%	88.0%	
More than once				
Count	2	0	2	
% within group	8.0%	0.0%	8.0%	1.000
More than twice				
Count	1	0	1	
% within group	4.0%	0.0%	4.0%	
Total				
Count	25	25	25	
% within group	100.0%	100.0%	100.0%	

*Chi-square test

Table 9: Cause of admission in ICU among different population

	Group R (n = 25)	*Group G (n = 25)*	*Group D (n = 25)*	*p-value**	
Medical no. (%)	17 (68%)	16 (64%)	19 (76%)	0.644	NS
Surgical no. (%)	8 (32%)	9 (36%)	6 (24%)		

*Chi-square test; NS, non-significant

insulin glargine that insulin degludec selection on the insulin dose reduction as well as their abilities to ensure a more stable glucose-lowering effect, which may facilitate titration and allow more tight control of the blood glucose level with a lower hypoglycemic episode.[17,18]

Conclusion

Long-acting as well as ultra-long-acting insulin compared to regular insulin can effectively control the RBS with a decrease in the total dose of insulin used as well as the incidence of hypoglycemia with no effect on the length of the ICU stay

Orcid

Ibrahim Mohammed El Sherif https://orcid.org/0000-0002-4635-9786
Adham Magdy Haggag https://orcid.org/0000-0002-7069-6707
Walid Y Kamel https://orcid.org/0000-0001-9573-3167

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