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Comparison of lispro insulin and regular insulin in the management of hyperglycaemic emergencies

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Summary

This study compared the efficacy and safety of Lispro insulin and regular insulin in the management of hyperglycemic emergencies (HE). Fifty patients who presented in HE to the Emergency unit of Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife participated in the study. Hyperglycaemic emergency was diagnosed when plasma glucose level was > 17 mmol/L (300 mg/dl) in the presence of polyuria and polydipsia that warrants emergency hospital admission. Subjects in the Lispro insulin group had a statum dose of 0.3 IU/kg, while those in the regular insulin group had a statum dose of 20 IU equally split between the intravenous and intramuscular routes. Further insulin therapy was by the intramuscular route. Data was analysed using the Statistical package for social sciences (SPSS) version 11. Hyperglycaemia resolved within the first 8 hours in 60 and 40% percent of subjects in the lispro and regular insulin treated groups respectively. The time taken for resolution of hyperglycaemia was similar in both treatment groups, 6.6±0.8 hours for the lispro insulin group and 7.4±0.8 hours for the regular insulin group p = 0.51. The number of episodes of hypoglycaemia and hypokalemia in the two treatment groups did not differ statistically (p = 1.0 and 0.38 respectively). Eight (16%) subjects died. Lispro insulin is a safe and efficacious alternative to regular insulin in the treatment of HE.

Keywords: *Hyperglycaemic emergency, Lispro insulin, Regular insulin.*

Résumé

Cette étude avait pour but de comparer l'efficacité et la sécurité de l'insuline Lispro et l'insuline régulière sur la gestion des urgences d'hyperglycémies (HE). Cinquante patients a l'unité d'urgence ayant des urgences d'hyper glycémiques dans le complexe universitaire Hospitalier d'Obafemi Awolowo, Ife participaient a l'étude. L'urgence hyperglycémique était diagnostiquée lorsque le taux du glucose sanguine était de > 17 mmol/L (300 mg/dl) en présence de la polyurie et polydipsie qui nécessitaient une admission hospitalière urgente. Les sujets dans le groupe de l'insuline Lispro avaient un dose de départ de 0.3 IU/kg, tan disque ceux dans le groupe de l'insuline régulier commençaient avec une dose de 20 IU partagée également entre les voies intraveineuse et intramusculaire ; Suivi de la thérapie a l'insuline était par voie intramusculaire. Les données étaient analysées en utilisant le logiciel SPSS version 11. Hyperglycémie se reconstituait dans les 8 heures chez 60 % et 40% aux groupes des sujets recevant l'insuline Lispro et régulier respectivement. Le temps mis pour la résolution de l'hyperglycémie était semblable aux deux groupes, 6.6 ± 0.8 heures pour le groupe recevant l'insuline lispro et 7.4 ± 0.8 heures pour le groupe recevant l'insuline régulier (p = 0.51). Le nombre des épisodes d'hypoglycémies et d'hypokaliémie chez les 2 groupes ne différenciaient pas statiquement (p = 1.0 et 0.38 respectivement). Huit (16%) des sujets mouraient. L'insuline Lispro est plus sécurisée et un alternatif efficace de l'insuline régulier pour le traitement des urgences hyper glycémiques.

Introduction

Hyperglycaemic emergencies (HE) are acute complications of diabetes associated with absolute or relative insulin deficiency, volume depletion and altered mental status severe enough to warrant emergency hospitalization [1]. They include Diabetic ketoacidosis (DKA), Hyperglycaemic hyperosmolar state (HHS), Lactic acidosis (LA) and Normo-osmolar nonketotic Hyperglycaemic state (NNHS), and are important causes of morbidity and mortality among patients with diabetes [2-4]. Hyperglycaemic emergencies are also an important cause of morbidity and mortality in Nigeria, due to poor drug compliance engendered by poverty, ignorance, poor health education, infection,

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delayed diagnosis, delayed treatment, poor laboratory support and omission of electrolyte monitoring especially potassium and at times erratic supply of essential drugs [4-6].

The standard treatment for patients with HE is the use of low- dose rapid-acting regular insulin [7]. The development of the short-acting insulin analogues lispro and aspart insulin in 1996, followed later by insulin glulisine provided added options for the treatment of HE as shown by Umpierrez et al [7,8]. Some studies have also shown that the intramuscular route may be efficacious in the management of HE [4,7,9-10].

This study tested the hypothesis that intermittent intramuscular insulin analogues are a safe and efficacious alternative to intermittent intramuscular regular insulin in the management of HE.

Materials and methods

This study was carried out at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), which comprises the Ife Hospital Unit (IHU) and Wesley Guild Hospital (WGH) Ilesa between October 2006 and September 2007. The Ethics and Research Committee of OAUTHC approved the study. The study was a prospective, randomized, open labelled, controlled clinical trial. Fifty-two consecutive patients admitted to the Accident and Emergency room who fulfilled the criteria for the diagnosis of hyperglycaemic emergencies selected by non-probability sampling technique [judgment sampling] were randomized assigned to receive either regular insulin or Lispro insulin.

The diagnosis of hyperglycaemic emergency was based on plasma glucose levels greater than 17mmol/l (300mg/dl) and the presence of symptoms of metabolic decompensation such as polyuria, polydipsia and weight loss [27]. The diagnosis of diabetic ketoacidosis (DKA) was based on plasma glucose levels greater than 17mmol/l (300mg/dl), significant ketonuria of 2+ or more and acidosis (serum bicarbonate less than 18mmol/L) in the presence of symptoms of metabolic decompensation such as polyuria, polydipsia and weight loss [3] while the diagnosis of hyperglycaemic hyperosmolar state (HHS) was based on random plasma glucose more than 25mmol/L (450mg/dl) and plasma osmolality greater than 320mosm/L with insignificant ketonuria in the presence of symptoms of metabolic decompensation like polyuria, polydipsia and weight loss [3].

The diagnosis of normo-osmolar nonketotic hyperglycaemic state (NNHS) was based on plasma glucose level greater than 17mmol/L (300mg/dl), calculated serum osmolality less than 320 mosm/L and absent or minimal (1+) ketonuria [3]. The diagnosis of mixed DKA and HHS was based on plasma glucose level greater than 17mmol/L (300mg/dl), serum osmolality greater than 320 mosm/L, serum bicarbonate level less than 15mmol/L and ketonuria of 2+ or more [11,12].

We excluded patients with congestive cardiac failure, end stage renal failure, hepatic failure, anasarca, pregnancy and dementia. Intravenous fluid and electrolyte replacement was performed by using normal saline at the outset and later 5% dextrose saline when blood glucose fell to13.8mmol/L (250mg/dl). Isotonic saline was given as 1 litre fast, then 1 liter over 30 minutes, then 1 litre over 1 hour, then 1 litre over 2 hours, then 500mls 4 hourly. Potassium replacement was performed when subjects were making urine and were not hyperkalaemic. When serum potassium was less than 3.5mmol/L, 40mmol potassium chloride (Kcl) was added to each litre of isotonic saline, when between 3.5mmol/L and 5.5mmol/L, 20mmol Kcl was added and when greater than 5.5mmol/L, Kcl was not added.

Insulin therapy was by the intramuscular route in an intermittent fashion in both treatment groups. For the regular insulin group, 20 units of regular insulin was given as a statum dose; 10 units intravenously and 10 units intramuscularly, followed by 6 units every hour until blood glucose fell to 13.8mmol/L (250mg/dl), thereafter, 6 units was given 4 hourly. Patients in the Lispro group had a statum dose of 0.3 units/ kg, equally split between the intramuscular and intravenous routes, followed by 0.1 units/ kg per hour intramuscularly until blood glucose fell to 13.8mmol/L (250mg/dl) when it was then reduced to 0.05 units/kg 2 hourly.

A peripheral vein was cannulated at presentation under sterile conditions and blood sample was collected for estimation of plasma glucose, urea, electrolytes, creatinine, packed cell volume and white blood cell count. Finger prick was done hourly for capillary blood glucose estimation with the glucometer, while for the purposes of quality control, venous blood was taken simultaneously at the 12th and 24th hour after commencement of therapy for plasma glucose level. Plasma potassium was checked at the 4th, 12th and 24th hours, while plasma urea, bicarbonate and creatinine were rechecked 24 hours after commencement of therapy. Urine was collected in a clean universal bottle for estimation of urine ketones, glucose, protein, pH

and nitrite using the dipstix. Plasma glucose levels were estimated according to Trinder's method using glucose oxidase solution. Hypokalemia was defined in this study as serum potassium less than 3 mmol/l while hypoglycemia was defined as blood glucose levels below 3.3 mmol/l (60mg/dl).

Statistical analysis was performed using the Statistical package for social sciences (SPSS) version 11. For comparison of categorical variable, chi-squared analysis was performed. Smaller proportions (with any cell less than 5) were compared using the Fisher's exact test. Comparison of means was by the student's t- test; 95% confidence interval was used to determine significance of probabilities and when $p < 0.05$, the difference was taken to be statistically significant. The standard error of the mean (SEM) was used to measure dispersion.

Results

A total of 52 subjects fulfilled the criteria for Hyperglycemic emergencies and were recruited into the study. Two of these discharged against medical advice and thus did not complete the study. Of the 50 subjects that completed the study, 25(50%) were males, while 25(50%) were females. Table 1 shows the Demographic and Anthropometric data of the study subjects. The subjects in both treatment groups were well matched for age, gender, and duration of diabetes, body mass index and waist circumference. The regular insulin group had a higher mean age, longer DM duration, higher BMI and WC though these did not reach statistical significance.

The types of hyperglycaemic emergencies were categorized into four: diabetic ketoacidosis (DKA), Hyperglycaemic hyperosmolar state (HHS), Normo-osmolar Non ketotic hyperglycaemic state (NNHS) and mixed DKA and HHS. Twenty five (50%) of the subjects fulfilled the criteria for HHS, 15(30%) subjects had NHHS while 5(10%) subjects fulfilled the criteria for DKA and a mixed picture of DKA and HHS respectively. Infection as the principal precipitating factor was found in 36(69%) subjects, of these, urinary tract infection was the commonest. No identifiable factors were discovered in 8(15.5%) of the subjects. One subject had both cerebrovascular disease and pneumonia as precipitating factors while a subject with foot infection also had concomitant pneumonia.

Table 2 shows the overall biochemical profile on admission and the biochemical profile in the two treatment groups. There was no statistically significant difference in the mean plasma glucose, potassium, bicarbonate, anion gap, osmolality, sodium, urea, creatinine and chloride in the two treatment groups.

Table 3 shows the response to therapy in the two treatment groups. In all, 26 (52%) subjects had random blood glucose less than 13.8mmol/L eight hours after commencement of therapy; fifteen (60%) of these were in the Lispro group while 11(44%) were in the regular insulin group. Eight hours after commencement of therapy 14(56%) subjects in the regular insulin group still had random blood glucose greater than 13.8mmol/L. Fifteen (60%) and 11(44%) subjects in the Lispro and regular insulin groups respectively had hyperglycaemia resolved within the first 8 hours of commencement of therapy. There was no statistically

Table 1: Demographic and Anthropometric profile of study subjects.

Characteristics	All subjects n=50	Lispro insulin group n=25	Regular insulin group n=25	p value
	Mean [SEM] or Number (%) [Range]			
Age (years)	53.8(2.0) [18-82]	52.3(3.1) [18-82]	55.2(2.5) [31-78]	0.45(NS)
DDM (months)	16.3(3.4) [0-78]	13.5(1.0) [0-72]	19.1(5.3) [0-78]	0.36(NS)
BMI (kg/m^2)	24.6(0.7) [15.7-35.3]	24.1(1.0) [16.4–33.9]	25.1(1.3) [15.7–35.3]	0.50(NS)
WC: Male	86.1(3.4) [60-119]	84.1(4.3) [60-115]	88.9(5.5) [62-119]	0.48(NS)
Female	89.0(2.6) [68-111]	88.5(3.5) [70-104]	89.5(3.9) [68-111]	0.84(NS)

BMI= Body mass index, DDM=Duration of diabetes, NS= Not significant, SEM= Standard error of the Mean, WC= Waist circumference.

Table 2: Biochemical profile on admission in the two treatment groups

Characteristics	All subjects n =50)	Lispro insulin group (n = 25)	Regular insulin group (n=25)	p value
	Mean (SEM) or Number (%) [Range]			
PG (mmol/L)	33.9(0.9) [23.1-49.2]	33.8(1.5) [23.1 -49.2]	34(1.2) [26.8-47.9]	0.92(NS)
Potassium (mmol/L)	4.2(0.1) [2.2-6.1]	4.2(0.1) [2.2-5.6]	4.1(0.1) [2.5-6.1]	0.41(NS)
Bicarbonate (mmol/L)	19.6(0.4) [10-29]	19(0.6) [10-26]	20.3(0.6) [10-29]	0.15(NS)
AG (mmol/L)	17(0.6) [8.2-30.2]	18(0.9) [8.2-28.2]	16(0.9) [9.1-30.2]	0.15(NS)
Osmolality (mOsm/L)	320.7(2) [281.5-357.2]	321(3.4) [281.5-357.2]	320.4(2.1) [303.1- 339]	0.89(NS)
Sodium (mmol/L)	134(0.7) [119-142]	134(1.1) [119-142]	133(1.0) [122-142]	0.89(NS)
Chloride (mmol/L)	101(0.6) [95-108]	101(0.8) [95-108]	101(0.8) [95-108]	0.84(NS)
Urea (mmol/L)	10.6(0.7) [4.1-22.6]	10.6(1.2) [4.1-22.6]	10.7(1.0) [4.2-20.7]	0.94(NS)
Cr (μmol/L)	217(19.2) [62-731]	215(23.2) [62-512]	219(30.9) [82-731]	0.91(NS)
Ketonuria	25(50)	14(56)	11(44)	
- Significant	10(40)	8(57)	2(18)	
- Insignificant	15(100)	6(43)	9(82)	

AG=Anion gap, Cr= Creatinine, mmol/L=millimoles/liter, mOsm/L=milliosmoles/liter, PG=Plasma glucose, NS= Not significant, SEM= Standard error of the Mean, μmol/L=micromoles/liter.

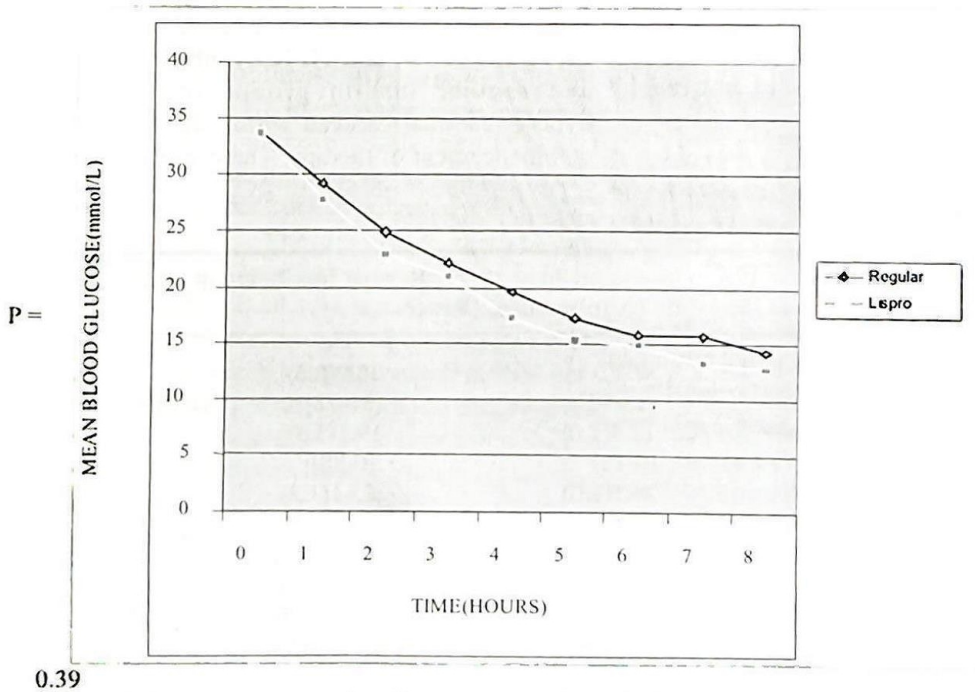

Fig. 1: Blood glucose response to insulin therapy within the first 8 hours in the two treatment groups

Table 3: Response to therapy in the two treatment groups

Variables	All subjects (n=50)	Lispro insulin group(n=25)	Regular insulin group(n=25)	p value
	Mean (SEM) or number (%) [Range]			
Hours taken to resolve hyperglycaemia	7.0(0.6) [1-16]	6.6 (0.8) [1-16]	7.4 (0.8) [2-16]	0.51(NS)
Mean rate of fall of blood glucose (mmol/hour)	4.6(0.4) [1.3 – 12.8]	5.0 (0.6) [1.4 – 11.8]	4.2(0.5) [1.3 – 12.8]	0.39(NS)
Blood glucose levels after first 8 hours:				
>13.8mmol/L	24(48)	10(40)	14(56)	
<13.8mmol/L	26(52)	15(60)	11(44)	0.82**(NS)
Amount of insulin needed to resolve hyperglycemia (unit)	58.0 (4.1) [18- 132]	56.4(6.0) [18-132]	59.6(5.5) [24-122]	0.68(NS)
Amount of insulin in first 24 hours (unit)	84.2 [32.164]	88.2(5.8) [40-164]	80.2(6.2) [32-134	0.35(NS)
Amount of fluid given in 24 hours(liters)	7.0(0.2) [5-11]	7.2(0.3) [5-10.5]	6.8(0.3) [5-11]	0.48(NS)
Amount of Potassium chloride used in 24hours (mmol)	50.2 (3.8) [20-120]	52.9 (5.8) [20-120]	47.4(4.9) [20-120]	0.47(NS)
Number of patients with episodes of hypoglycemia	5(10)	3(12)	2(8)	1.0*(NS)
Number of patients with episodes of hypokalemia	10(20)	7(28)	3(12)	0.28*(NS)
Duration of admission (days)	11(1.1) [1-34]	10(1.5) [1-34]	12(1.5) [1-31]	0.47(NS)

**Fishers exact test, **: X2= 2.92,df=1, NS= Not significant, SEM= Standard error of the Mean*

significant difference in the mean number of hours taken to resolve hyperglycaemia (p= 0.51), mean rate of fall of blood glucose (p = 0.39), mean amount of insulin required to resolve hyperglycaemia (p = 0.68) and that required in the first 24hours (p= 0.35). Three (12%) subjects in the Lispro insulin group and 2(8%) in the regular insulin group had hypoglycaemic episodes during the first 24 hours of insulin therapy while 7(28%) and 3(12%) subjects in the Lispro and regular insulin treatment groups respectively had episodes of hypokalaemia. In all, eight (16%) subjects died, four (16%) each in both treatment groups. Figure 2 shows the mean blood glucose in the two treatment groups in the first 8 hours of therapy. The mean blood glucose level reduced progressively in the two treatment groups. There was no statistically significant difference in the mean rate of fall of blood glucose in the two treatment groups.

A total of 8 subjects died, seven of them in the HHS group and 1 in the NNHS group. The mortality rate for HHS was 28% while that for NNHS was 6.7%. The case fatality rate in this study was 16%. Seven (88%) of the subjects that died were male, giving a male mortality rate of 28% while 1 female patient died giving a female mortality rate of 4%. Although the mean age of non-survivors of 60±3.7 years was higher than that of survivors, it did not reach statistical significance. Similarly, there was no statistically significant difference in the mean duration of diabetes of survivors and non-survivors. There was no significant difference between

the mean plasma glucose at presentation, osmolality, anion gap, time taken to resolve hyperglycaemia, mean rate of fall of blood glucose, serum sodium, potassium, bicarbonate, and chloride of survivors and non-survivors. Serum urea and creatinine were higher in non –survivors than in survivors but this was not statistically significant.

Five of the eight subjects that died had early deaths (death within the first four days of admission). All the deaths were due to sepsis and complications that follow it especially the adult respiratory distress syndrome (ARDS). One of the subjects that died due to sepsis also had late diagnosis and initiation of treatment as major contributors to the demise. Two late deaths were due to hypoglycaemia 5 days after admission in one case and 11 days after admission in the other case. One subject died 15 days after admission from a repeat cerebrovascular disease.

Discussion

Our results showed similar hyperglycaemia resolution time in the two treatment arms. This compares with the observations of Umpierrez *et al* [7,13] using subcutaneous insulin Lispro/aspart and intravenous regular insulin in the management of DKA in a sample of American patients. Ehusani *et al* [9] and Oli [10] in separate studies in Nigeria had previously reported resolution of hyperglycaemia within 6-8 hours of commencing intermittent intramuscular regular insulin. The mean rate of fall of blood glucose was also similar in the two treatment groups. The minimum 10% glucose decrement [14] expected to occur in the first hour of insulin therapy was achieved in 76% of the Lispro group and 60% of the regular insulin group. Fisher *et al* [14] reported that 30 – 40% of subjects on intramuscular insulin attained 10% reduction in glycaemia in the first hour of therapy.

A comparable quantity of insulin was required to resolve hyperglycaemia in the Lispro and regular insulin treated groups. Umpierrez *et al* [22] also found no significant difference in the amount of insulin required to resolve hyperglycaemia. Hypoglycaemia still constitutes one of the potential complications of insulin therapy. Hypoglycemic episodes during the acute management of HE occurred at the same rate with Lispro and regular insulin treatment in our study. Though Umpierrez *et al* [7]. observed a slightly lower rate of hypoglycemic episodes, Ehusani et al[9] observed no hypoglycemic episodes. The incidence of hypoglycaemia during the acute phase of management can be reduced by the commencement of dextrose containing fluids when blood glucose reaches 13.8 mmol/l (250mg/dl) with concomitant reduction in the frequency of insulin administration. Fatal hypoglycaemia should ideally not complicate hyperglycaemic emergency treatment.

Hypokalaemia was observed at presentation in some patients in this study. Initial hypokalaemia in hyperglycaemic emergencies indicate unusually severe total body potassium depletion but even this is not uncommon, since hyperglycaemia leads to osmotic diuresis and renal loss of water and electrolytes. In the United States, Abramson and Arky [15] reported initial hypokalaemia in 3 patients with diabetic ketoacidosis while Beigelman [16] reported 4% of DKA patients seen as having hypokalaemia at presentation.

The impact of hypokalaemia as a potential cause of morbidity and mortality due to arrhythmias during treatment of hyperglycaemic emergencies had been highlighted by Abramson *et al* [15] and Talabi [17].

Hypokalaemia does occur during the acute management of hyperglycaemic emergencies as shown by our data. This is however not uniformly observed, for instance Umpierrez *et al* [7] did not observe any episode of hypokalemia in their study. It is known that insulin administration, correction of acidosis, and volume expansion following rehydration leads to a decrease in serum potassium concentration during therapy of hyperglycaemic crisis [2,3]. The incidence of hypokalaemia is markedly diminished with low dose insulin therapy [14].

There was no difference between the mean duration of admission and hospital stay for the two treatment groups in this study though there was a tendency towards longer hospital stay among our patients when compared with data from Umpierrez *et al* [7,13]. An important factor in the duration of admission is the precipitating factor. Subjects with foot ulcers as the precipitant in this study stayed on admission for more than 30 days in most instances. Ehusani [9] had also previously made this observation in subjects who had septic foot ulcers as the precipitant of the hyperglycaemic crisis in Lagos.

Morbidity and mortality still does occur even in developed countries following development and management of hyperglycaemic emergencies though at a much lower rate than observed in Nigeria [18,19].

The higher morbidity and mortality rates in developing countries are attributable to late presentation in hospital, paucity of medical facilities and personnel [6,20]. The mortality rate in this study was 16% (same for both treatment groups). This is much lower than the rate of 56% reported from our institution over a decade ago and 60% close to a decade ago [21,22] It is also lower than that reported from Lagos by Ehusani *et al* [4] and later Ogbera *et al* [23] as well as from Ilorin by Okoro *et al* [24].

Our study has some limitations; the sample size in this study was small, blood ketones, glycosylated haemoglobin, serum pH, lactate, and bedside ECG monitoring to detect hypo- or hyperkalaemia could not be done in this study because of lack of facilities. Our results indicate that use of Lispro insulin is a viable, safe and efficacious alternative in the treatment of hyperglycaemic emergencies in Nigeria.

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