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COMPARISON OF INSULIN GLARGINE AND GLULISINE WITH INSULIN NPH AND REGULAR FOR GLYCEMIC CONTROL IN CHILDREN WITH TYPE –I DIABETES MELLITUS

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Abstract:

Introduction*: Among the various types of insulin analogs, some are long acting and some are short acting. Neutral Protamine Hagedorn (NPH) is one of the intermediate acting insulin analog with about 16 hours of duration of action with a peak between 6-14 hours. NPH is given with Regular (R) insulin, short acting insulin analogue with peak in 3-5 hr and duration of action till 8 hours.*

Objectives*: To compare mean HbA1c level in type 1 diabetes mellitus children on glargine + glulisine basal bolus regimen with neutral protamine hagedorn (NPH) + regular insulin.*

Study design*: Randomized controlled trial*

Settings: Pediatrics Unit-II and III ward, emergency and outpatient department, Allied Hospital, Faisalabad

Study duration: 5th June 2017 to 4th January 2018

Materials & Methods*: A total of 120 children of both genders of 5 to 15 years with type-I diabetes mellitus were included. Patients with type I diabetes with complications like diabetic ketoacidosis, celiac disease, mucocutaneous candidiasis, Addison's disease and hypoparathyroidism and Cushing's disease were excluded. Patient in group A was given glargine once daily and glulisine was given with each meal three times daily. Patients in group B were given NPH insulin and regular insulin twice daily before meals. Dose of insulin was calculated according to age and weight and given subcutaneously. Each patient was followed after 3 months through their contact numbers. HbA1c level was done one the first day and repeated after 3 months.*

Results*: Mean age was 9.63 ± 2.68 years. Out of 120 patients 79 (65.83%) were males and 41 (34.17%) were females with male to female ratio of 1.9:1. Mean HbA1c level in type 1 diabetes mellitus children in Group A (glargine + glulisine basal bolus regimen) was 6.30 ± 0.62 while in Group B ((NPH) + regular insulin) was 7.12 ± 0.64 (p-value = 0.0001).*

Conclusion*: This study concluded that children with type-I diabetes mellitus treated with insulin glargine as long acting insulin along with Insulin glulisine as ultra-short acting insulin have lower HbA1c than those taking NPH and regular insulin.*

Keywords: *Type-I Diabetes Mellitus, Insulin Glargine, Regular Insulin.*

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INTRODUCTION:

Type I Diabetes Mellitus is second name for Insulin dependent diabetes mellitus. Its incidence among pediatric age group is increasing across the world, around a third these presents with diabetic ketoacidosis.1 It is managed by administering exogenous insulin, dietary modification, various life style changes and regular monitoring of the blood sugar level. Among the acute complications of this disease, hypoglycemia and diabetic ketoacidosis (DKA) are most common and deadly ones. Just an improvement of glycemic control can prolong the healthy life of a diabetic patient.2,3. Among the various types of insulin analogs, some are long acting and some are short acting. Neutral Protamine Hagedorn (NPH) is one of the intermediate acting insulin analog with about 16 hours of duration of action with a peak between 6-14 hours. NPH is given with Regular (R) insulin, short acting insulin analogue with peak in 3-5 hr and duration of action till 8 hours. It should be administered at least before 30 mins from the meal, which is often not possible for children because they can't wait. Children on regular insulin often have hypoglycemic intervals between the meals and more chances of nocturnal hypoglycemia.4-10 Like Lispro, Glulisine is also a very rapid-acting insulin analog given along with every meal in basal bolus regimen along with a long acting insulin analog like glargine. When given subcutaneously, it appears in the blood earlier than human insulin and its effects remains for 2-4 hours.3,10 van Bon AC, et al. reported after clinical trials on glulisine, aspart and lispro insulin that there was no significant difference between these three with respect to unexplained hyperglycemia.7 The latest insulin analogs like glargine and glulisine mimic insulin action and also promote glucose uptake into skeletal muscle and adipose tissue and decreases the rate of gluconeogenesis, glycogenolysis and lipolysis.8 Glargine is an insulin analog with long duration of action (roughly 24 hrs with no peak). It causes lesser hypoglycemia when compared to NPH. After the subcutaneous injection it slowly moves into the blood and produces the desired effects.9-12

Children on basal bolus regimen using glargine and glulisine have a better 24 hour glycemic control with lesser hypoglycemic episodes between the meals and during the night.12 Philotheou A, et al. reported that rapid-acting insulin analogs can be administered much closer to the meals because of extended absorption from tissue than regular insulin. After the clinical trial he reported that 38.4% of the children on glulisine reached their target improve HbA1c level as compared to 32% children in lispro group.13 American Diabetes Association (ADA) recommends HbA1c levels < 7%, while the American Association of Clinical Endocrinologists and the International Diabetes Federation recommends HbA1c target of < 6.5%.3 Mianowska B, et al. reported that glycosylated hemoglobin level was lower (7.1±0.16) in diabetic children on basal bolus regimen of glargine with glulisine than the glycosylated hemoglobin of children on NPH with regular insulin (7.71±0.25).14 Adhikari S, et al. reported HbA1c 6.6 ± 1.1 after 3 months on glargine regimen as compared to 7.2 ± 1.2 HbA1c after 3 months of NPH regimen.5 Yanagisawa K, et al reported that by switching to glulisine insulin for 24 weeks with basal insulin glargine significantly decreased level of HbA1c.15

MATERIALS & METHODS:

STUDY DESIGN: Randomized controlled trial.
SETTING: Pediatrics Unit-II and III ward, emergency and outpatient department, Allied Hospital, Faisalabad.
DURATION OF STUDY: 5th June 2017 to 4th January 2018.
SAMPLE SIZE: Calculated according the who calculator for sample size using mean and standard deviation for two groups.
Sample size: 60 patients in each group (total 120)
SAMPLE TECHNIQUE: Non-probability, consecutive sampling.
SAMPLE SELECTION: Inclusion Criteria:

- All children of both genders of 5 to 15 years with type-I diabetes mellitus without any other autoimmune disease were included in the study.
- New and old cases of DM.

b. Exclusion Criteria:

- Children with type I diabetes with complications like diabetic ketoacidosis
- Children of type I diabetes along with celiac disease, mucocutaneous candidiasis, Addison's disease and Hypoparathyroidism and Cushing's disease.

After proper approval from the ethical review committee (ERC), patients of type I diabetes meeting the inclusion criteria were included in the study after written informed consent form the parents. Each patient was evaluated and relevant data was collected to meet the inclusion and exclusion criteria. All the patients inducted in the study were randomly divided into two groups by using computer generated number. Patient in group A was given glargine once daily and glulisine was given with each meal three times daily. Patients in group B were given NPH insulin and regular insulin twice daily before meals. Dose of insulin was calculated according to age and weight and

given subcutaneously. All the parents / guardians were educated regarding how to check blood glucose level at home, how to administration of insulin subcutaneously, how to keep record of blood glucose levels and what are the signs of hypoglycemia. Each patient was followed after 3 months through their contact numbers. HbA1c level was done one the first day and repeated after 3 months. All the data was collected on a preformed questionnaire.Data was analyzed using SPSS version 19. Mean and standard deviation were calculated for quantitative variables like age, weight and HbA1c at baseline and after 3 months. Frequency and percentages were calculated for qualitative variables like gender, diagnosis of diabetes and family history. Independent samples t-test was used to compare the mean HbA1c at baseline and 3 months after treatment. P-value < 0.05 was taken as statistically significant. Effect modifiers like age, gender, baseline HbA1c, family history and diagnosis of diabetes were controlled by stratification. Post stratification independent sample t-test was applied. P-value < 0.05 was taken as statistically significant.

RESULTS:

Age range in this study was from 5 to 15 years with mean age of 9.63 ± 2.68 years. The mean age of patients in group A was 9.78 ± 2.82 years and in group B was 9.60 ± 2.62 years. Majority of the patients 70 (58.33%) were between 5 to 10 years of age as shown in Table I. Out of 120 patients 79 (65.83%) were males and 41 (34.17%) were females with male to female ratio of 1.9:1 as shown in Figure I. Mean Baseline HbA1c was 8.01 ± 0.93. The mean Baseline HbA1c in group A was 8.00 ± 0.94 and in group B was 8.03 ± 0.92. Majority of the patients 82 (68.33%) were between >7 Baseline HbA1c as shown in Table II. Distribution of patients according to diagnosis of DM and family h/o DM is shown in Table III & IV respectively. Mean HbA1c level in type 1 diabetes mellitus children in Group A (glargine + glulisine basal bolus regimen) was 6.30 ± 0.62 while in Group B ((NPH) + regular insulin) was 7.12 ± 0.64 as shown in Figure II (p-value = 0.0001). Stratification of HbA1c level with respect to age groups and gender is shown in Table V & VI which showed significant difference in mean HbA1c level in all age groups and gender among both groups. Similarly statistically significant difference was found in mean HbA1c level in different Baseline HbA1c levels among both groups as shown in Table VII. Stratification of HbA1c level with respect to diagnosis of DM and family h/o DM is shown in Table VIII & IX respectively which also showed statistically significant difference among different groups.

Table-I: Age distribution for both groups (n=120).

	Group A (n=60)		**Group B (n=60)**		**Total (n=120)**	
Age (years)	No. of patients	%age	No. of patients	%age	No. of patients	%age
5-10	34	56.67	36	60.0	70	58.33
11-15	26	43.33	24	40.0	50	41.67
Mean ± SD	**9.78 ± 2.82**		**9.60 ± 2.62**		**9.63 ± 2.68**	

Figure-I: Distribution of patients according to Gender (n=120).

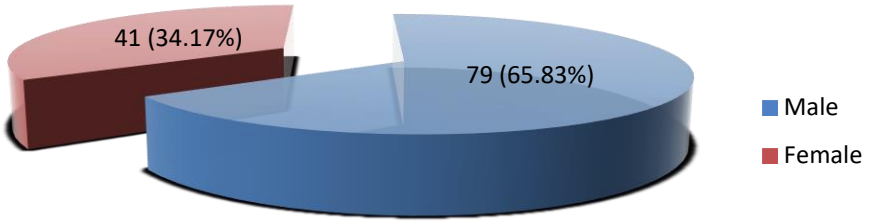


Table-II: Distribution of patients according to Baseline HbA1c.

Baseline HbA1c	Group A (n=60)		Group B (n=60)		Total (n=120)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤7	18	30.0	20	33.33	38	31.67
>7	42	70.0	40	66.67	82	68.33
Mean ± SD	**8.00 ± 0.94**		**8.03 ± 0.92**		**8.01 ± 0.93**	

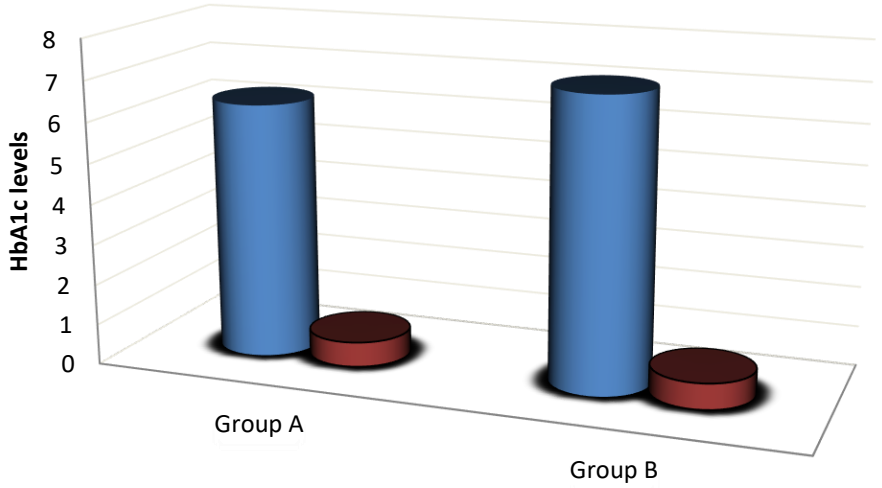
Table-III: Distribution of patients according to diagnosis of DM.

Diagnosis of DM	Group A (n=60)		Group B (n=60)		Total (n=120)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
New	38	63.33	39	65.0	77	64.17
Old	22	36.67	21	35.0	43	35.83

Table-IV: Distribution of patients according to family history of DM.

Family history of DM	Group A (n=60)		Group B (n=60)		Total (n=120)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
Yes	41	68.33	38	63.33	79	65.83
No	19	31.67	22	36.67	41	34.17

Figure II: Mean HbA1c level in type 1 diabetes mellitus children in both groups.



	Group A	Group B
Mean	6.3	7.12
Standard Deviation	0.62	0.64

- P-value = 0.0001 which is statistically significant

Table V: Stratification of HbA1c level with respect to age groups.

Age of patients (years)	Group A (n=60) HbA1c level		Group B (n=60) HbA1c level		P-value
	Mean	SD	Mean	SD	
5-10	6.21	0.64	7.28	0.70	**0.0001**
11-15	6.42	0.78	6.88	0.45	**0.0137**

Table VI: Stratification of HbA1c level with respect to gender.

Gender	Group A (n=60) HbA1c level		Group B (n=60) HbA1c level		P-value
	Mean	SD	Mean	SD	
Male	6.30	0.69	7.13	0.66	**0.0001**
Female	6.30	0.47	7.10	0.63	**0.0001**

Table VII: Stratification of HbA1c level with respect to Baseline HbA1c.

Baseline HbA1c	Group A (n=60) HbA1c level		Group B (n=60) HbA1c level		P-value
	Mean	SD	Mean	SD	
≤7	5.94	0.24	6.70	0.47	**0.0001**
>7	6.45	0.67	7.32	0.62	**0.0001**

Table VIII: Stratification of HbA1c level with respect to diagnosis of DM.

Diagnosis of DM	Group A (n=60) HbA1c level		Group B (n=60) HbA1c level		P-value
	Mean	SD	Mean	SD	
New	6.34	0.53	7.13	0.73	**0.0001**
Old	6.23	0.75	7.10	0.44	**0.0001**

Table IX: Stratification of HbA1c level with respect to family h/o DM.

Family h/o DM	Group A (n=60) HbA1c level		Group B (n=60) HbA1c level		P-value
	Mean	SD	Mean	SD	
Yes	6.29	0.64	7.16	0.68	**0.0001**
No	6.32	0.58	7.05	0.58	**0.0003**

DISCUSSION:

According to International Diabetes Federation (IDF) an estimated 387 million people (8.3% of adults) had Diabetes Mellitus (DM) in 2014; and by 2035, 592 million are expected to be inflicted with DM. Although type 1 diabetes mellitus (T1DM) accounts for 5%-10% of diabetes cases, its incidence is increasing by 3% annually. The landmark 'Diabetes Control and Complications Trial' (DCCT) shows that compared to conventional therapy, intensive insulin therapy effectively delays the onset and slows the progression of micro- and macrovascular complications and reduces overall mortality in patients with T1DM.100 However, hypoglycemia and weight gain are the main limiting factors with insulin use in patients with T1DM.101 In this context, there is a need for insulin regimens that overcome these barriers and achieve optimal glycemic control with low risk of hypoglycemia. Basal-bolus insulin therapy usually involves administration of basal insulin (with a stable 24-h serum insulin profile) and meal-time rapid-acting insulin to cover both fasting and pre-prandial glucose requirements of the patient. However, conventional intermediate and long-acting human basal insulins are limited with a pronounced peak in time-action post injection and large variability in absorption.102 Regular insulins on the other hand show slower onset and more prolonged action than endogenous insulin secretion. Together, the combination results in high postprandial blood glucose excursions, and is often associated with 2-3 fold increase in severe hypoglycemia.101

Amongst long-acting insulin analogs, intensive treatment with insulin glargine (IGlar) is found to be superior to intermediate-acting NPH in T1DM patients, with significant reduction in HbA1c and frequency of hypoglycemic events.103 While long-acting insulin analogs, IGlar and insulin detemir (IDet) show similar pharmacokinetic and pharmacodynamic effects during the first 12 h of administration, IGlar shows superior effects extending up to 24 h.104 Additionally, once daily (OD) IGlar achieves similar glycemic control and comparable risk of hypoglycemia to that of twice daily IDet, each in combination with pre-meal insulin aspart.105 Further,

patients with diabetes, inadequately controlled by premixed insulin, switching from premixed insulin to IGlar based regimen experience significant improvement in glycemic control, supporting the use of basal-bolus glargine-based regimen in these patients.106 Studies on combination of IGlar OD and multiple mealtime rapid-acting insulins, as part of basal-bolus therapy in T1DM patients demonstrate improved overall glycemic control and reduced nocturnal hypoglycemia.107 However the appropriate rapid-acting insulin analog for combination with IGlar that provides effective glycemic control and low risk of hypoglycemia in T1DM patients is not established.108 In few open-label studies, insulin glulisine (IGlu) and insulin lispro, both in combination with IGlar show similar reduction in HbA1c but with a lower total daily dose of IGlu.109-111 Further, replacement of bolus insulin with IGlu in T1DM patients uncontrolled on intensive therapy with (basal) IGlar+(bolus) aspart/lispro/ regular human insulin, demonstrates improved glycemic control for 24 weeks.108.

I have conducted this study to compare mean HbA1c level in type 1 diabetes mellitus children on glargine + glulisine basal bolus regimen with neutral protamine hagedorn (NPH) + regular insulin. Age range in this study was from 5 to 15 years with mean age of 9.63 ± 2.68 years. The mean age of patients in group A was 9.78 ± 2.82 years and in group B was 9.60 ± 2.62 years. Majority of the patients 70 (58.33%) were between 5 to 10 years of age. Out of 120 patients 79 (65.83%) were males and 41 (34.17%) were females with male to female ratio of 1.9:1. Mean HbA1c level in type 1 diabetes mellitus children in Group A (glargine + glulisine basal bolus regimen) was 6.30 ± 0.62 while in Group B ((NPH) + regular insulin) was 7.12 ± 0.64 (p-value = 0.0001). Mianowska B, et al. reported that glycosylated hemoglobin level was lower (7.1±0.16) in diabetic children on basal bolus regimen of glargine with glulisine than the glycosylated hemoglobin of children on NPH with regular insulin (7.71±0.25).14 Adhikari S, et al. reported HbA1c 6.6 ± 1.1 after 3 months on glargine regimen as compared to 7.2 ± 1.2 HbA1c after 3 months of NPH regimen.5 Yanagisawa K, et al reported that by switching to glulisine insulin for 24 weeks with basal insulin glargine significantly decreased level of HbA1c.15.

In randomized clinical trials, IGlar appears to improve glycemic control in terms of HbA1c and FBG reduction compared to NPH insulin, with added advantage of lower risk of hypoglycemia and weight gain.112,113 Similarly in cross-over trials comparing IGlar to NPH, IGlar was associated with a mean decrease in HbA1c ranging from -0.5%107 to -0.7%.114 When compared to detemir, IGlar provides similar glycemic control with a mean decrease in HbA1c of -0.5% after 26 weeks105 which is maintained up to one year.115 In a study116, sub-optimal glycemic control was evident from higher study-end HbA1c and FBG values compared to recommended targets for good glycemic control. Despite significant decrease in HbA1c from baseline, the mean ± SD HbA1c after 24 weeks of treatment was 8.5% ± 1.3%, which is well above the target specified by international guidelines (<7%). Similarly, though a significant (p<0.001) reduction in FBG was achieved as early as 12 weeks, the study-end FBG levels (8.3 ± 4.4 mmol/L) were considerably higher than desired targets to be achieved (4.5 to 6.7 mmol/L).116 Appropriate insulin dose titration is crucial in achieving good glycemic control in T1DM patients.117,118.

Three clinical trials compared all-analog insulin regimens to all-human insulin regimens.119-121 In the largest, a basal-bolus regimen of insulin aspart/insulin detemir was compared with NPH insulin/regular insulin in 595 patients with type 1 diabetes for 18 weeks.119 At study end, mean HbA1c was lower in the aspart/detemir group compared with the NPH/regular insulin group (7.88% vs. 8.11%; P<0.001). In a smaller but longer study of 56 type 1 subjects, a regimen of glargine plus lispro was associated with a mean HbA1c of 7.5% after 32 weeks compared to 8.0% with a regimen of NPH plus unmodified human insulin.121 In the third study, a crossover design study of 28 adolescent subjects, there was no significant difference in HbA1c between subjects treated with glargine/lispro and those treated with NPH/regular insulin, each for 16 weeks (8.7% vs. 9.1%; P=0.13).120.

In a multicentre, randomized, single-blind (a blinded investigator made titration decisions) study122, 125 patients received preprandial insulin lispro and either glargine (n = 62) or NPH (n = 63) at bedtime for 30 weeks. Basal insulin dosage was titrated to achieve fasting blood glucose (FBG) values < 5.5 mmol/L. Baseline characteristics were similar for the two groups (mean diabetes duration 17.5 +/- 10.1 years) except mean glycated haemoglobin (HbA(1c)), which was lower in the glargine versus NPH group (9.2 +/- 1.1% vs 9.7 +/- 1.3%; P < 0.02). At end-point, mean HbA(1c) was 8.3 versus 9.1% for the glargine versus NPH groups. Adjusted least-squares mean (LSM) change from baseline was -1.04 versus -0.51%, a significant treatment benefit of 0.53% for HbA(1c) in favour of glargine (P < 0.01). Mean baseline FBG

were similar for the glargine and NPH groups (11.2 vs 11.4 mmol/L). The means for end-point FBG were 7.9 versus 9.0 mmol/L. Adjusted LSM change from baseline was -3.46 versus -2.34 mmol/L, with a significant difference of 1.12 mmol/L in favour of glargine (P < 0.05). There were similar total numbers of daytime mild, moderate or severe hypoglycaemia episodes in the two treatment arms. However, significantly fewer moderate or severe nocturnal hypoglycaemic episodes were observed in the glargine group (P = 0.04 and P = 0.02).122

In another study123, a total of 51 patients with type 1 diabetes on intensive therapy (NPH four times/day and lispro insulin at each meal) were randomized to three different regimens of basal insulin substitution while continuing lispro insulin at meals: continuation of NPH four times/day (n = 17), once daily glargine at dinnertime (n = 17), and once daily glargine at bedtime (n = 17) for 3 months. Blood glucose targets were fasting, preprandial, and bedtime concentrations at 6.4-7.2 mmol/l and 2 h after meals at 8.0-9.2 mmol/l. The primary end point was HbA(1c). Mean daily blood glucose was lower with dinnertime glargine (7.5 +/- 0.2 mmol/l) or bedtime glargine (7.4 +/- 0.2 mmol/l) versus NPH (8.3 +/- 0.2 mmol/l) (P < 0.05). A greater percentage of blood glucose values were at the target value with glargine at dinner and bedtime versus those with NPH (P < 0.05). HbA(1c) at 3 months did not change with NPH but decreased with glargine at dinnertime (from 6.8 +/- 0.2 to 6.4 +/- 0.1%) and glargine at bedtime (from 7.0 +/- 0.2 to 6.6 +/- 0.1%) (P < 0.04 vs. NPH). Total daily insulin doses were similar with the three treatments, but with glargine there was an increase in basal and a decrease in mealtime insulin requirements (P < 0.05). Frequency of mild hypoglycemia (self-assisted episodes, blood glucose < or =4.0 mmol/l) was lower with glargine (dinnertime 8.1 +/- 0.8 mmol/l, bedtime 7.7 +/- 0.9 mmol/l) than with NPH (12.2 +/- 1.3 mmol/l) (episodes/patient-month, P < 0.04). In-hospital profiles confirmed outpatient blood glucose data and indicated more steady plasma insulin concentrations at night and before meals with glargine versus NPH (P < 0.05).123

In a study124, a total of 197 patients were randomized to receive glargine/glulisine therapy (n = 106) or premixed analogue therapy (n = 91). Overall, the mean age was 56 years, the mean duration of diabetes was 13 years, with a mean HbA(1c) of 9.25% and mean BMI of 35.8 kg/m(2) at baseline. Patients randomized to receive glargine/glulisine had a greater mean HbA(1c) reduction from baseline (-2.3%) than patients receiving a premixed analogue regimen (-1.7%). Adjusted mean follow-up HbA(1c) was 6.9% versus 7.5%, respectively (difference, -0.59%; P < 0.01). The glargine/glulisine group also used a lower mean number of OADs (0.86 vs 1.14; difference, -0.28; P = 0.04) but had a higher weight (240 vs 235 lb; difference, 4.55 lb; P = 0.03) than the premixed analogue group at follow-up. There were no significant differences in daily insulin dose and rates of hypoglycemia.124

CONCLUSION:

This study concluded that children with type-I diabetes mellitus treated with insulin glargine as long acting insulin along with Insulin glulisine as ultra-short acting insulin have lower HbA1c than those taking NPH and regular insulin. So, we recommend that with insulin glargine as long acting insulin along with Insulin glulisine as ultra-short acting insulin should be used as primary treatment regimen in type 1 diabetes mellitus children in order to achieve the good glycemic control.

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