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Original Article

A Pilot Study of the Use of Insulin Glargine in Combination with Short Acting Insulin Analogue in Adolescents with Type I Diabetes Mellitus in Hong Kong

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Abstract This pilot study is a retrospective analysis of the frequency of nocturnal hypoglycaemia and glycaemic control in 7 adolescents with well-controlled type I diabetes 3 to 6 months before and 6 months after switching to a new long-acting insulin analog-insulin glargine in combination with short acting insulin analogues before meals. The patients were on short acting insulin before the three main meals and isophane insulin at bedtime and they had a mean annual HbA1c value of 7.6±0.4%. The patients were switched to a new regime of insulin lispro before the three main meals and insulin glargine at bedtime. The mean duration of glargine treatment was 0.8±0.3 years. The mean average fasting blood glucose determined by glucometer was significantly improved from 9.9±1.4 mmol/L to 8.5±1.2 mmol/L ($p<0.05$) after switching to insulin glargine. The proportion of morning blood glucose between 4 to 10 mmol/L achieved by patients significantly increased from 42.7±11.2% to 52.2±15.2% ($p<0.05$) without nocturnal or morning hypoglycaemia. There was no significant change in the daily insulin dosage between the two treatment regimes. This combination has a high degree of acceptability to motivated adolescent patients. A larger prospective study on the beneficial effects of insulin analogues on poorly controlled diabetes is warranted.

Key words Adolescents; Insulin glargine; Type I diabetes mellitus

In a normal individual, pancreatic B cells secrete a basal amount of insulin between meals and a larger amount after meals. Basal-bolus insulin regimens attempt to reproduce the function of a healthy pancreas and supply exogenous insulin in a similar fluctuating pattern in patients with type I diabetes mellitus (DM). The disadvantages of conventional short- and intermediate-acting insulin preparations include variable absorption with considerable intra and inter-subject variation, pronounced peaks after injections, and prolonged duration of action, all contributing to the difficulty in obtaining normoglycaemia.[1]

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Insulin glargine is a new long-acting insulin analogue produced through recombinant DNA technology with substitution of glycine for asparagine at position A-21 and the extension of the C-terminal of the B-chain by two arginine residues in positions B-31 and B-32 leading to an increase in the isoelectric point.[2,3] As a result of the shift in the isoelectric point, insulin glargine is less soluble at the injection site and precipitates subcutaneously to form a depot, from which insulin is slowly released.[4] Insulin glargine has an onset of action 1 hour after subcutaneous administration.[5] Full activity is reached within 4 to 5 hours and persists at a constant level for 24 hours.[6,7] Insulin Glargine has been used as the basal insulin in combination with a rapidly acting insulin analogues such as insulin lispro or insulin aspart as the bolus insulin given with meals to mimic closely the human physiological insulin secretion pattern, especially in type I DM patients who have no endogenous insulin production.

Several clinical trials have shown that insulin glargine can significantly decrease the number of severe and nocturnal hypoglycaemic episodes in both type I and

type II DM patients. However, the use of insulin glargine has not yet been demonstrated to lead to better overall glycaemic control compared to regimes using isophane insulin. This article reviews the experience of the use of insulin glargine in combination with premeal short-acting insulin analogues in a group of adolescents with well-controlled type I diabetes mellitus.

Patients and Method

A total of 7 motivated patients (6 girls and 1 boy) with well-controlled type I diabetes, aged 11-18 years, were started on insulin glargine obtained by self-purchase. Medical records of the patients were reviewed to assess diabetic control before and after use of insulin glargine. Their clinical characteristics are described in Table 1.

Prior to initiation of insulin glargine therapy, all patients were on intensive insulin regime of four injections daily (soluble insulin before the three main meals and isophane insulin at bedtime). Their injections were monitored through self-record of blood sugar measurements 2-5 times daily by a glucometer. The new regime consists of insulin glargine given at bedtime and regular insulin was replaced by insulin lispro before meals. The diets were readjusted with removal of the mid-morning and mid-afternoon snacks but keeping the snack before bed. The daily caloric intake and carbohydrate allowance remained unchanged. After changing over to insulin glargine, these subjects were monitored intensively 5 times daily and adjustment of glargine dosage until the control of the diabetic state was stable usually within 2 to 3 weeks.

The primary outcome variables included frequency of nocturnal hypoglycaemia, frequency of high (>13 mmol/L) and low blood sugar (<4 mmol/L), changes of fasting blood glucose and the mean morning blood sugar before and after the switching over to insulin glargine therapy. The comparison was made between three to six months prior to (baseline) and six months following insulin glargine therapy. Analysis of blood glucose records of each patient began from the second month after the starting of insulin glargine allowing one month for stablisation of insulin dosage. Other outcome measures included change in haemogoblin A1c one year prior to and subsequent to starting of insulin glargine (mean of 3 readings but only two HbA1c readings were available in patient 7) and frequency and severity of hypoglycaemia.

Nocturnal hypoglycaemia was defined as symptomatic hypoglycaemia occurring in the subjects between bedtime and the morning injection as dextrostix was not routinely measured in these children except during the period of stablisation. Haemoglobin A1c was measured in whole blood by an affinity cation-exchange high performance liquid chromatographic method on the Variant II analyzer (Diagnostics Group, Bio-Rad Laboratories, CA, USA) and reference value of the haemoglobin A1c method used in Queen Mary Hospital is between 4.3% and 6.2%. Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia in which the subject required assistance of another individual and was either accompanied by a blood glucose level <2.2 mmol/l or had prompt recovery after oral glucose, intravenous glucose, or glucagons administration.

Data are reported as mean and standard deviation. Data were analysed by analysis of variance followed by Student's paired T-test. A p-value of 0.05 or less is regarded as statistically significant.

Table 1 Clinical characteristics of patients

Total number of patient in study	7
Male : Female ratio	1 : 6
Mean age (years)	13.2±2.4
Mean duration of type I DM (years)	8.6±3.7
Mean annual HbA1c (%)	7.6±0.4
Mean insulin dose (IU/kg/day)	1.29±0.26

Results

Subjects

Six girls and one boy with type I diabetes mellitus were started on insulin glargine in combination with insulin lispro. The average age was 13.2±2.4 years and average age of onset of diabetes was 4.6±3.2 years. The duration of diabetes was 8.6±3.7 years while the duration of insulin glargine was 0.8±0.3 years. All of the patients received insulin glargine at bedtime.

Haemoglobin A1c Levels and Home Blood Glucose Monitoring

The mean average haemoglobin A1c level over one year period prior to initiation of insulin glargine therapy was 7.6±0.4%. After changing over to insulin glargine therapy, the average haemoglobin A1c was 7.4±0.3% but this difference was not significant (p=0.64) (Table 2) .

The mean of the average fasting blood glucose levels determined by glucometer among seven patients were

Table 2 Haemoglobin A1c (%), mean morning blood sugar level (mmol/l), and total insulin dosage (IU/kg) before and after the initiation of insulin lispro/glargine

Patient	HbA1c (%)		Mean morning blood sugar (mmol/l)		Mean insulin dosage (IU/kg)	
	Before	After	Before	After	Before	After
1	7.3±0.5	6.7±0.2	11.11	9.39	1.35	1.19
2	7.0±0.3	7.9±0.7	9.18	10.27	1.20	1.26
3	8.2±0.6	8.6±0.1	9.22	8.41	1.38	1.82
4	7.6±0.4	6.9±0.2	9.29	6.94	1.48	1.23
5	8.3±0.5	7.1±0.4	9.83	8.86	0.97	0.93
6	7.9±0.1	7.5±0.2	12.43	8.71	1.65	1.33
7	6.7±0.1	7.3	8.24	7.03	0.97	0.79
Mean±SD	7.6±0.6	7.4±0.6	9.90±1.41	8.52±1.20	1.29±0.26	1.22±0.33
p-value	0.64		0.048		0.53	

significantly improved from 9.90±1.41 mmol/l to 8.52± 1.20 mmol/l after the introduction of insulin glargine, ($p<0.05$) (Table 3). On lispro/glargine therapy, the proportion of morning blood glucose greater than 13.0 mmol/l decreased significantly from 29.6±12.3% to 16.5± 7.65% ($p<0.05$). Similarly, the proportion of morning blood glucose between 4.0 mmol/l and 10.0 mmol/l achieved by the patients significantly increased from 42.7±11.2% to 52.2±15.2% ($p<0.05$). However, the proportion of fasting blood glucose levels less than 4 mmol/l observed in our patients did not change significantly, (12.8±7.9% vs 13.1±7.7%). The results of the fasting blood sugar monitoring before and after changing to insulin glargine are shown in Table 2.

Insulin Dosage

The total insulin dosage before and after switching to insulin glargine among these patients did not show a significant change, 1.29±0.26 unit/kg, while using conventional insulin regime, to 1.22±0.33 unit/kg ($p=0.53$). After changing over to insulin glargine therapy, no significant change was seen in long-acting insulin dosages (0.44 unit/kg vs. 0.42 unit/kg; $p=0.83$). The dosage of short-acting insulin (0.73 unit/kg vs 0.80 unit/kg) and the ratio of short- to long-acting insulin doses were similar on each regimen ($p=0.21$ and 0.42, respectively).

Adverse Effects

No severe hypoglycaemic event or nocturnal hypoglycaemia were reported by the patients before or after the initiation of insulin glargine therapy. However, one patient had encountered frequent mild exercise induced hypoglycaemia after switching over to insulin lispro and glargine. He improved on changing over to novorapid instead of lispro as rapid-acting insulin analogue. The patients noticed no other severe adverse effects except one

Table 3 Proportion of high and low fasting blood glucose level (percentage) documented in the patients before and after the initiation of insulin lispro/glargine

Patient	Blood sugar <4 mmol/l		Blood sugar 4-10 mmol/l		Blood sugar >13 mmol/l	
	Before	After	Before	After	Before	After
1	9.78	10.46	31.52	48.37	42.39	21.57
2	23.60	8.94	37.08	39.02	28.09	28.49
3	21.51	18.35	41.94	47.71	29.03	13.76
4	2.15	2.94	59.14	82.35	16.13	5.88
5	14.61	9.80	38.20	53.59	31.46	15.69
6	5.56	23.33	33.33	36.67	46.67	20.00
7	12.09	22.38	57.41	57.34	13.19	9.79
Mean±SD	12.8±7.9	13.7±7.7	42.7±11.2	52.2±15.2	29.6±12.3	16.5±7.6
p-value	0.81		0.03		0.04	

patient experienced slight pain during the injection of insulin glargine. All patients revealed that the switch to insulin lispro had allowed them to eat their meal immediately after injection and this was regarded as improvement in their quality of life.

Discussion

Ratner et al compared the effectiveness and efficacy of insulin glargine and isophane insulin in adult patients with type I DM for up to 28 weeks.[8] This multi-centre trial involved 534 well-controlled type I DM patients. In the insulin glargine group, fewer incidents of severe hypoglycaemia and nocturnal hypoglycaemia where blood glucose was less than 2.0 mmol/L were reported. Although there were no significant changes in glycaemic control found in both groups, a greater reduction in median fasting plasma glucose was observed in patients on insulin glargine. Similar findings were observed in similar trials involving 333 adult type I DM patients over 4 weeks[9] and 619 type I DM patients over 66 weeks.[10] A recent trial involving 121 type I DM patients comparing the combination use of insulin glargine and insulin lispro and the combination of isophane insulin and insulin lispro over 1-year period.[11] Significantly fewer cases of both symptomatic and nocturnal hypoglycaemia were observed in the insulin glargine group. Also, there was a significant improvement in glycaemic control in the glargine group compared to the isophane group.

A multi-centre, open-labelled, randomised trial involving 349 type I DM children and adolescents aged between 5-16 years, compared the effect of insulin glargine and isophane insulin.[12] Both the change in HbA1c and overall incidences of hypoglycaemia were similar in the two groups of patients but fasting plasma glucose was lower in those who were using insulin glargine. Although a reduced number of severe and nocturnal hypoglycaemia episodes was observed in the insulin glargine group, this did not achieve statistical significance. In another study involving 114 children with type I DM, insulin glargine therapy resulted in a decrease in mild and severe hypoglycaemic episodes without jeopardising glycaemic control.[13] Insulin glargine given once daily under supervision had been shown to improve glycaemic control in poorly controlled children and adolescents with type I DM.[14]

The major limitation of this report is that this is a retrospective review of a pilot study of the use of insulin glargine in a limited number of well-controlled type I diabetes patients. The most significant finding in this study is that the mean morning blood sugar as documented by home blood glucose monitoring with glucometer improved after the initiation of insulin lispro/glargine therapy. However, this study did not show any significant change in the frequency of symptomatic hypoglycaemia or change in haemoglobin A1c. There was a significant decrease in proportion of morning blood sugar greater than 13 mmol/l. The significant fall in the mean fasting blood sugar from 9.9±1.4 mmol/l to 8.8±1.1 mmol/l was achieved without any significant increase in incidence of nocturnal hypoglycaemia and proportion of morning blood sugar below 4.0 mmol/l. Importantly, the proportion of morning blood sugar between 4.0 mmol/l and 10.0 mmol/l achieved by these patients was significantly improved. This result suggested that insulin lispro/glargine therapy allowed the diabetic individual to have a better control of blood glucose level overnight than the conventional NPH insulin regime. Our results are consistent with findings of previous published studies involving greater number of patients.[12-14]

Whether insulin lispro/glargine combination therapy would result in better glycaemic control reflected by haemoglobin A1c could not be answered in the present small study. All of the patients included in this study had good glycaemic control and were motivated and compliant with the treatment. Glycaemic control depends on multiple factors including insulin regime, compliance with insulin therapy, dietary habit, activity level, motivation of the patients, and support from peers and family members.

A meta-analysis involving 2,576 type I diabetic patients demonstrated that the frequency of severe hypoglycaemia was reduced in patients with type I diabetes by taking insulin lispro.[15] Large snacks compromise preprandial glycaemic control and mid-morning and mid-afternoon snacks are inconvenient to adolescents. Conventional soluble insulin has to be given 30 minutes before meals and most adolescents find this inconvenient and difficult to comply especially on eating out.[16,17] After starting on the new insulin therapy, patients did not need to worry about intake of snacks in between meals and were able to eat immediately after the injection, resulting in an improvement in the quality of life of these adolescents.

As with all new drugs, there are always concerns of the long-term safety of insulin glargine. Insulin glargine has about 50-60% the affinity of human insulin for the insulin receptor and a six-fold increased affinity for IGF-1 receptors and an eight-fold greater ability to promote DNA synthesis as compared with human insulin.[18] Concern has been raised since IGF-1 signaling is known to promote vascular

endothelial growth factor dependent neurovascularization. One 6-month study in patients with type II diabetes resulted in more frequent progression of retinopathy with insulin glargine[19] but the finding was not observed in other studies.[10,12] These concerns should be addressed further in future long-term studies. One patient has experienced mild injection site pain but this did not result in cessation of insulin glargine treatment. Injection site pain occurred more frequently with insulin glargine than NPH insulin since insulin glargine is more acidic. A major drawback is the high cost of the new insulin analogue.

Conclusion

In conclusion, insulin lispro/glargine combination provides a stable basal insulin supply using glargine and matching the meals with injections of short acting analogues. This insulin regime provides an insulin profile which better mimicks that of normal individuals than what could be provided by daily injections of regular insulin before meal and NPH-insulin before bed. The lispro/glargine combination has a high degree of acceptability to motivated adolescents with type I diabetes. A larger prospective study of the beneficial effect of the use of insulin analogues in poorly controlled diabetic patients is warranted.

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