responses to treatment including ritonavir or nelfinavir in HIV-1-infected children. Pediatric AIDS Group of Switzerland. Infection 2000; 28: 287-296.

12. Saez-Llorens X, Violari A, Deetz CO, Rode RA, Gomez P, Handelsman E, *et al.* Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22: 216-224.
13. Melvin AJ, Lewis PF, Mohan KM, Naugler WS, Frenkel LM. Efficacy and toxicity of antiretroviral therapy using 4 or more agents: application of a strategy for antiretroviral management in human immunodeficiency virus-infected children. Arch Pediatr Adolesc Med 2002; 156: 568-573.
14. McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A. First Pediatric Switch Study. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. Pediatrics 2003; 111: e275-e281.
15. Johnston AM, Valentine ME, Ottinger J, Baydo R, Gryszowka V, Vavro C, *et al.* Immune reconstitution in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy: A cohort study. Pediatr Infect Dis J 2001; 20: 941-946.
16. Verweel G, van Rossum AM, Hartwig NG, Wolfs TF, Scherpbier HJ. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. Pediatrics 2002; 109: E25.

Concomitant Use of Insulin Glargine and NPH in Type I Diabetes

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In a prospective study on 11 patients with Type 1 diabetes we evaluated the glycaemic control and hypoglycaemic episodes on a combination therapy of "pre-mixed" and glargine insulin. Glycosylated hemoglobin (HbA_{1C}), fasting (FPG) and Post Prandial blood glucose (PPG) levels were recorded at baseline and three monthly intervals for a period of 6 months. The mean HbA_{1C} reduced from 9.5 to 7.3%, incidence of hypoglycemias from 1.6 to 0.8, mean FPG from 146.5 to 90.4 and mean PPG from 258.4 to 184 over a six-month observation period. This regimen also helps to avoid injection of insulin before lunch so that child's school schedule is minimally disturbed and yet the incidence of hypoglycemia is not increased.

Key words: *Glycosylated hemoglobin, Insulin glargine, Type 1 diabetes.*

INSULIN Glargine is a long acting analogue of insulin, which has a peakless profile and has been used successfully in the management of type 1 diabetes in combination with short or ultra short acting insulin preparations(1). It has been shown to reduce the incidence of nocturnal hypoglycemia and is at least as effective as NPH in controlling Glycosylated hemoglobin (HbA_{1C})(2,3). In most clinical trials insulin glargine is used as basal insulin along with 3 or 4 doses of short or ultra short acting insulin. The disadvantage of this regimen is that a minimum of 4-5 injections per day have to be administered, very frequent blood sugar monitoring becomes mandatory and the cost of monitoring and therapy together is quite high. We studied the glycemic control in type I diabetic children using a combination of partial "pre-mixed", short acting and glargine insulin and also the safety of this combination in terms of hypoglycemia. We used a novel combination of NPH, short acting and glargine insulin to reduce the number of injections, partly reduce the cost of treatment while achieving better control of HbA_{1C} and blood sugars thus potentially reducing long term complications. Reports of the use of Insulin glargine in type 1 diabetes are rare in Indian literature, hence this report.

Subjects and Methods

Eleven patients with Type I diabetes between the age of 7 and 15 years were studied. At the beginning of the study all children were on "pre-mixed"(4) *i.e.*, 2 daily doses of combination of short and intermediate acting insulins (in proportion of 2/3 intermediate acting and 1/3 short acting) given as before breakfast and before dinner doses. At the beginning of study period all 11 children's regimen was changed to before breakfast combination of short acting and NPH insulin (1/3 and 2/3 dose respectively) and before dinner combination of short acting and Glargine insulin, Glargine being given as a separate injection at a separate site. No insulin injection was given before lunch. Patients were asked to perform home monitoring of blood glucose (HMBG) on three days of the week and keep a diary and were requested to report to the clinic every month. Performance checks were made on patient's glucometers at each of these monthly visits. HbA_{1C} was performed by High Performance Liquid Chromatography (HPLC). Parameters studied included height, weight, HMBG readings, Glycosylated hemoglobin (HbA_{1C}) and number of symptomatic hypoglycemic episodes at baseline, 3 months and 6 months period.

Ethical committee of our research institute approved the study and all patients' assent and parents signed informed consent was obtained before the study was started.

Results

Of the 11 patients studied, 7 were females and 4 were males. Mean age of patients at the time of starting insulin glargine was 11.2 years and mean duration of diabetes was 3.9 years (6 months to 8 years). The dose of glargine used at the beginning was 0.2 units/kg/day and increased to 0.3 units/kg/day at 3 months interval due to higher than acceptable fasting glucose and HbA_{1C} levels. Mean daily dose of insulin was 0.9 µ/kg at baseline, it was 1 µ/kg at 3 months and remained the same at the end of 6 months of therapy. Two patients dropped out of the study after 3 months of therapy as they found 3 injections (as opposed to two of pre-mixed insulin) hard to take. Wilcoxon Signed rank test was applied to the HbA_{1C} performed on the 9 patients and a significant difference was found in the HbA_{1C} at baseline and six months. The same test was applied to the body mass index standard deviation scores (BMISDS) at baseline and six months of

therapy and no significant difference was found in the BMISDS.

As can be seen in *Table I* the HbA_{1C} , fasting and post prandial plasma glucose levels reduced after 6 months of therapy (mean FPG at baseline-146.5 mg/dL, at 6months- 90.4, mean PPG at baseline –258.4, at 6 months 184 mg/dL).

The decline in plasma glucose levels, incidence of hypoglycemia and decline in HBA_{1C} is shown in (*Figs. 1-3*) respectively. There was a reduction in mean number of hypoglycemia's from 1.6 to 0.5 at three months to become 0.8 at 6 months. This was possibly due to the fact that one patient was inadvertently given double the dose of insulin resulting in a hypoglycemic episode. No nocturnal hypoglycemias were noted.

Discussion

Insulin Glargine is a recombinant analogue of regular insulin that is produced by adding two arginine molecules at the end of B chain and substitution of one glycine unit in place of aspargine at position 21 on the A chain. This insulin is soluble in acidic medium but precipitates in the neutral pH of subcutaneous tissue forming small particulate hexamers, which slowly get absorbed in the circulation. It thus provides approximately 24 hours of peakless insulin mimicking the natural basal pancreatic secretion.

In the early years of Type 1 diabetes as there is some preservation of circulating natural insulin still present, pre-mixed or two daily injections of combination of short acting and intermediate acting insulin are often given to control sugars. This regimen gives four peaks of insulin thus providing cover for mealtime hyperglycemia as well as basal insulin. The downside of this regimen is that it produces night time hypoglycemia due to late peak that NPH produces following pre dinner dose. As the duration of Type 1 diabetes increases there is near total absence of endogenous insulin and hence after first few years "pre-mixed" regimens are not ideal. Glargine is an ideal long acting insulin to control hyperglycemia in between meals and when coupled with 3-4 injections of regular or lispro insulin before meals it is a most successful regimen (besides Continuous Subcutaneous Insulin therapy [CSII]) in controlling hyperglycemia. This regimen also prevents night time hypoglycemia and it has been shown in large trials such as DCCT that with such multidose regimens it is possible to postpone the complications of diabetes(5). Insulin glargine has been shown to be better than twice-daily ultralente or NPH in

TABLE I–*Mean Values of Study Parameters*

	Baseline	3 months	6 months
Glycosylated hemoglobin(%)	9.5	9.1	7.3
Hypoglycemic episodes	1.6	0.5	0.8
Glargine dose (unit/kg/d)	0.19	0.3	0.3
Short acting insulin dose/kg	–	0.21	0.21
"Premixed" insulin dose/kg	0.9	0.49	0.49
Total insulin/day in µ/kg	0.9	1.0	1.0
Fasting plasma glucose (mg/dL)	146.5	119	90.4
Post prandial glucose (mg/dL)	258.4	259	184

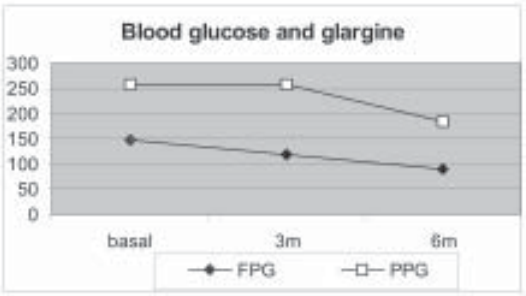

Fig. 1. The decline in plasma glucose levels was from 146.5 to 90.4 mg/dl (fasting) and 254.4 to 184.0 mg/dl (post prandial) after six months of therapy.

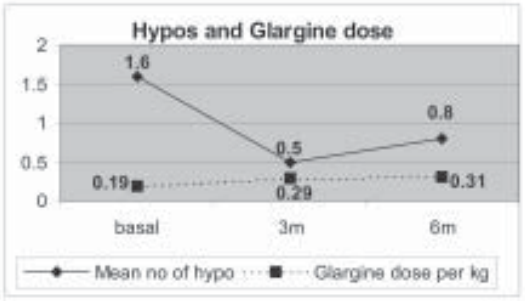

Fig. 2. Reduction in mean number of hypoglycemias was from 1.6 to 0.5 at three months to become 0.8 at six months.

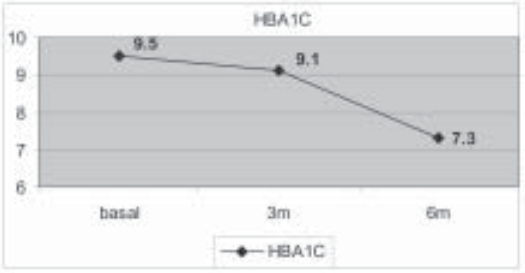

Fig. 3. HbA1C reduced from 9.5 at baseline to 7.3 at six months.

controlling HbA_{1C}, and in some studies it has been shown to control fasting plasma glucose better than NPH. It comes closest to CSII, which is the gold standard in insulin therapy today(6) and use of Glargine has been shown to reduce the incidence of hypoglycemia in general and nocturnal hypoglycemia in particular(2).

In India there are many restrictions on use of intensive therapy, which include exorbitant cost of newer insulin analogues, lack of 24 hours access to diabetes clinic, patients', parents and teachers' inability to accept the demanding life style due to HMBG and multiple injections. Long school hours and reluctance of parents to use injections in the school premises adds to the problems.

We used a regimen, which consisted of before breakfast combination of short acting and NPH insulin thus giving 2 peaks during daytime, one following breakfast and second following lunch. This eliminates the need for before lunch insulin injection and also allows for in between meal snacking, which is common in children. The second set of injections was used before dinner as a combination of short acting insulin and glargine at two separate sites. This provided cover for post dinner hyperglycemia and baseline insulin cover for 24 hours was provided by glargine. As no NPH was used at dinnertime there was no danger of late night insulin surge causing hypoglycemia. NPH during daytime along with glargine increased the level of circulating insulin during waking hours but as most children eat 4-5 times during the day, increased incidence of hypo-glycemias during the day was not noted. Weight gain was a concern but was not observed in our patients, as was seen from the BMISDS, possibly because the total dose of insulin remained almost constant before and after initiation of glargine. Glargine is an expensive insulin at present and its cost (about Rs 2/unit) increases further due to short shelf life after opening the vial. Vials are only available in 1000 units thus increasing the wastage. Prefilled pen cartridges which are available abroad will be welcome to make it more affordable for our patients.

Key Message

- A combination of glargine insulin with NPH and short acting insulin may allow better Glycemic control without increasing hypoglycemic episodes thus reducing the risk of long-term complications.

Our study shows that concomitant use of Glargine and NPH is possible. Fasting and post meal sugars as well as HbA_{1C} was better controlled in our patients thus potentially reducing long term complications. The lowering of the HbA_{1C} may also partly be attributed to the greater scrutiny of the patients by the parents and the study team. Three injections per day was acceptable to most patients and smaller vials or pre filled cartridges will help to reduce wastage and improve cost effectivity.

Contributors: VVK and AVK carried out the clinical workup. AVK collected the data and both authors drafted the manuscript. VVK will act as guarantor of the study.

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Competing interests: Nil.

REFERENCES

1. Owens DR, Griffiths S. Insulin glargine (Lantus). Int J Clin Pract 2002, 56: 460-466.
2. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000, 23: 639-643.
3. Pieber TR, Eugene-Jolchine I, Derobert E. The European Study Group of HOE 901 in type 1 diabetes. Efficacy and safety of HOE Diabetes Care 2000, 23: 157-162.
4. Virmani A, Bhatia V. Ambulatory Management of Diabetes Mellitus. *In:* Desai MP, Bhatia V, Menon PSN. Pediatric Endocrine Disorders, 1st edn. Chennai, Orient Longman, 2001; p 312-319.
5. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993, 329: 977-986.
6. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, *et al*. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000, 49: 2142-2148.