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A Randomized, Controlled Trial Comparing Twice-a-Day Insulin Glargine Mixed With Rapid-Acting Insulin Analogs Versus Standard Neutral Protamine Hagedorn (NPH) Therapy in Newly Diagnosed Type 1 Diabetes

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ABSTRACT

OBJECTIVE. Insulin glargine is difficult to use for children due to the number of injections required because it is claimed to be immiscible with rapid-acting insulin analogs. For this study, we hypothesized that treating new-onset type 1 diabetes with twice-daily insulin glargine plus a rapid-acting insulin analog mixed in the same syringe would result in better glycosylated hemoglobin than twice-daily neutral protamine Hagedorn with a rapid-acting insulin analog (standard treatment).

METHODS. Forty-two patients with new-onset type 1 diabetes were started on standard treatment. Three months after diagnosis, if patients were found compliant and had a glycosylated hemoglobin level of $\leq 9\%$, then they were randomly assigned either to receive insulin glargine twice daily mixed with a rapid-acting insulin analog or to continue on standard treatment for 3 more months. Additional lunchtime rapid-acting insulin analog injections were given for the insulin glargine group as necessary.

RESULTS. Nineteen patients in the insulin glargine group and 17 in the neutral protamine Hagedorn group completed the study. The glycosylated hemoglobin level at baseline was $6.8\% \pm 1\%$ vs $6.9\% \pm 1\%$ and at poststudy was $6.7\% \pm 1.3\%$ vs $7.6\% \pm 1\%$ in the insulin glargine versus neutral protamine Hagedorn group, respectively. Two patients in the insulin glargine group required lunch rapid-acting insulin analog in the last month of the study. Although both groups were encouraged to contact the principal investigator with all queries, more in the insulin glargine arm opted to do so.

CONCLUSIONS. Glycemic control with insulin glargine mixed with a rapid-acting insulin analog given twice daily seems significantly more effective than the standard therapy in newly diagnosed type 1 diabetes. Furthermore, it decreases pain and burden of injections for children with diabetes by allowing patients to mix glargine with rapid-acting insulin analog.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00206401).

Key Words

children, diabetes, insulin

Abbreviations

DCCT—Diabetes Control and Complications Trial

GHb—glycosylated hemoglobin

NPH—neutral protamine Hagedorn

RAIA—rapid-acting insulin analog

BG—blood glucose

IG—insulin glargine

PI—principal investigator

QoL—quality of life

FBG—fasting BG

LBG—prelunch BG

SBG—presupper BG

PedsQL—Pediatric Quality of Life Inventory

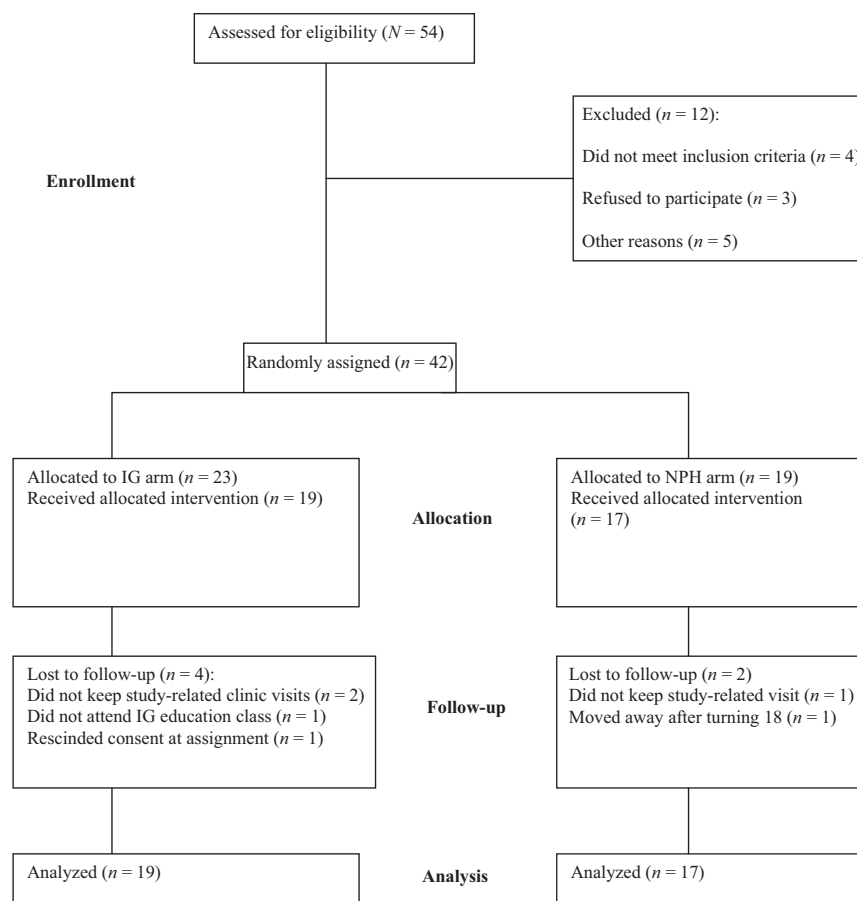
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GOOD GLYCEMIC CONTROL reduces the risk for retinal, renal, and neuropathic complications in patients with type 1 diabetes.¹ In fact, the Diabetes Control and Complications Trial (DCCT) reported that any improvement in glycosylated hemoglobin (GHb) levels contributed toward a reduction in microvascular complications.² Unfortunately, in children with type 1 diabetes, achieving and maintaining optimal glycemic control is a challenging process; this in the midst of demands of normal development and puberty.³ Glycemic control is reflective of adherence to a treatment regimen. In children, the primary obstacle to optimal glucose control is the number of insulin injections required to achieve the DCCT-recommended glycemic goals.^{1,4} The conventional therapy for children with type 1 diabetes at onset is twice-daily injections of neutral protamine Hagedorn (NPH) insulin mixed with a rapid-acting

FIGURE 1
Participant flow.



insulin analog (RAIA).⁵ NPH peaks at 4.5 ± 0.5 hours⁶ and is associated with an increased risk for nocturnal hypoglycemia.¹ RAIA's lispro and aspart are absorbed faster than NPH, improving 1-hour and 2-hour postprandial blood glucose (BG) levels⁷; however, long-term improvement in glycemic control is better achieved with the simultaneous, optimal replacement of basal insulin using either the insulin pump or multiple daily insulin injections.⁷

Insulin glargine (IG), a long-acting insulin analog, is considered a "basal insulin"⁸ that is "peakless" and has a flat concentration/action profile that closely mimics the profile of insulin pump therapy, the gold standard of basal insulin replacement.⁶ Furthermore, the duration of action of IG is said to last 24 hours,^{9,10} requiring patients to take only a once-a-day injection. There are very limited data on IG pharmacokinetics in pediatric patients. In children with type 1 diabetes, clinical observations indicate that IG action may be <24 hours.^{11,12} Ashwell et al¹³ demonstrated that BG concentrations were lower with twice-daily IG as compared with a once-daily IG regimen. Furthermore, restrictions cautioned by the manufacturers of IG against mixing IG with RAIA would result in 2 injections before breakfast and 2 injections before dinner with possibly an additional injection at lunch. This treatment regimen would pose a challenge to pediatric patients in maintaining treatment adherence.¹⁴

In our previous report,¹⁵ we demonstrated that divid-

ing the total daily dosage of IG into prebreakfast and predinner injections mixed with lispro/aspart insulin in the same syringe with an RAIA given at lunch did not adversely affect BG concentrations. In this randomized, controlled trial, we compared the effect of twice-daily IG mixed with an RAIA versus twice-daily NPH mixed with an RAIA during a 3-month period in patients with new-onset type 1 diabetes. We hypothesized that twice-daily IG plus RAIA would result in superior glycemic control than the standard therapy of twice-daily NPH plus RAIA in our pediatric population. We further hypothesized that mixing the RAIA with IG in the same syringe would not have deleterious effects on glycemic control.

METHODS

The institutional review board at Baylor College of Medicine approved the protocol. The study was a single-site study at Texas Children's Hospital (Houston, TX), in which all study-related visits took place at the outpatient clinic of the department of endocrinology and metabolism. Participants in this study included children who had a new diagnosis of type 1 diabetes and were aged 6 to 21 years (see Fig 1). Patients were included when they had received the diagnosis <3 months earlier, were found to be positive for at least 1 antibody (islet cell or insulin antibody or antibody to glutamic acid decarboxylase), had a BMI \leq 90th percentile at screening, had a GHb level of \leq 9% at 3 months after diagnosis, and were

willing to be randomly assigned. Both the patient and legal guardian had to be fluent in English, and the legal guardian needed to be present at the screening visit. Patients were not included when they had type 2 diabetes or any other chronic illness, had a history of chemical abuse, took medication besides insulin that had the potential to alter BG readings, lacked a supportive family, and a GHb level of $>9\%$ was seen after the initial 3-month run-in period.

At screening and on confirmation that the patient first received the diagnosis <3 months earlier, consent and assent were obtained from the legal guardian and the patient, respectively, by the principal investigator (PI) or a research associate who was involved in this study. GHb was obtained, and BMI percentile was calculated by using height and weight measurements. Patients were supplied with a FreeStyle Flash meter (Therasense Inc, Alameda, CA) for BG measurement and a 3-month supply of strips and lancets. Patients were instructed to test blood sugar levels at least 4 times a day, prebreakfast, prelunch, predinner, and once a week at 2 AM. If patients were concerned about their blood sugar readings, then they were advised to call/e-mail the PI only.

Three months after diagnosis, if the GHb level tested at $\leq 9\%$, then patients were randomly assigned using a random-number table that was computer-generated by a statistician. Each eligible patient was allocated to receive either IG mixed with RAIA or NPH mixed with RAIA by the research coordinator at his or her respective clinic visit. Allocation was sequential as dictated by the random-number table. Neither the study patients nor the research personnel were blinded to group assignment. When patients were randomly assigned to receive NPH with RAIA, patients continued as previously instructed and returned to clinic 3 months later. When patients were randomly assigned to IG with RAIA, patients attended a class on how to use IG, mix IG with an RAIA, and calculate insulin dosages accurately based on insulin:carbohydrate ratio and insulin sensitivity factor only, with no reiteration of previously taught material. Patients discontinued use of NPH the morning after class and started using IG instead. All interventions were self-administered, in compliance with study and self-management guidelines.

Total daily IG dosage was the same as the NPH dosage at the time of the changeover; IG replaced NPH unit for unit at breakfast and dinner. When mixing the insulin, the RAIA was drawn into the syringe first followed by the IG. Dosage changes were made according to pattern management whenever necessary. When blood sugar levels were high or low throughout the day, both breakfast and supper doses of IG were either increased or decreased, respectively. IG dosage was increased at supper to adjust high morning blood sugar levels. High predinner blood sugar levels warranted the increase in morning IG, after which persistent high blood sugars before dinner necessitated the introduction of a lunchtime injection of an RAIA. This was found to be necessary for only 2 patients of the IG arm. This lunchtime dose was calculated on the basis of the 450 rule (450/

total daily dose = grams of carbohydrates covered by 1 U of Humalog/Novolog).

All patients in both groups counted carbohydrates and were taught to appropriate insulin doses for meals. As such, meal plans were not fixed, but overeating of carbohydrates above the recommended amounts/meal was not encouraged. Snacks of ≤ 15 g of carbohydrates were allowed in the meal plan.

All of these patients were also to return to the clinic 3 months later. All participating patients were given another 3-month supply of strips and lancets.

At the last study-related visit 6 months after diagnosis, GHb levels were measured, BG readings were downloaded from the FreeStyle meter, and vials of used insulin were returned to ensure compliance. All study participants and legal guardians were required to answer a questionnaire each to compare quality of life (QoL) of patients between the 2 study arms. The primary outcomes of this study was GHb level, and secondary outcomes were BG control, insulin dosage, BMI, hypoglycemia, and QoL.

Measures

GHb Levels

GHb levels were analyzed by using the Bayer (Bayer Inc, Tarrytown, NY) 2000+ spectrophotometer.¹⁶

Blood Glucose Levels

Fasting BG (FBG), prelunch BG (LBG), and presupper BG (SBG) levels for each patient were calculated from data downloaded from the FreeStyle Flash meters. FBG, LBG, and SBG levels during a 2-week period leading up to the clinic visits at 3 and 6 months were obtained and averaged for each patient and each treatment group.

Hypoglycemia

Information on hypoglycemic episodes (BG < 2.7 mmol/L) was gathered solely from data downloaded from the FreeStyle Flash meter.

Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales

The 23-item PedsQL Generic Core Scales^{1,17-19} encompass (1) physical functioning (8 items), (2) emotional functioning (5 items), (3) social functioning (5 items), and (4) school functioning (5 items). Child self-report includes ages 5 to 18 years, and parent proxy report includes ages 2 to 18 years. The items for each form are essentially identical. The instructions ask how much of a problem each item had been during the past 1 month. A 5-point response scale is used (0 = never a problem, 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, and 4 = almost always a problem). Items are reverse-scored and linearly transformed to a scale from 0 to 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0); higher scores indicate a better QoL. Scale scores are computed as the sum of the items divided by the number of items answered. If 50% of the items in the scale are missing, then the scale score is not computed. The physical health summary score (8 items) is the same

TABLE 1 Clinical Characteristics Before Versus After the Study

Characteristic	IG (n = 19)	NPH (n = 17)	P ^a
Age, y	11.8 ± 3.7	10.1 ± 2.0	.080
BMI, kg/m ²	21.5 ± 5.1 vs 21.1 ± 4.1 (P < .7)	20.5 ± 3.2 vs 21.3 ± 3.6 (P < .01)	.900
GHb, %	6.8 ± 1.0 vs 6.7 ± 1.3 (P < .7)	6.9 ± 1.0 vs 7.6 ± 1.0 (P < .05)	.027
Insulin, U/kg	0.5 ± 0.2 vs 0.8 ± 1.3 (P < .4)	0.8 ± 0.3 vs 0.6 ± 0.2 (P < .05)	.500
FBG, mmol/L	6.6 ± 1.7 vs 6.1 ± 1.5 (P < .2)	7.2 ± 1.3 vs 10.6 ± 4.5 (P < .02)	.008
LBG, mmol/L	8.3 ± 4.6 vs 7.2 ± 3.4 (P < .3)	8.0 ± 2.7 vs 8.7 ± 4.9 (P < .60)	.800
SBG, mmol/L	7.1 ± 2.5 vs 7.9 ± 3.5 (P < .5)	10.4 ± 4.9 vs 10.4 ± 5.9 (P < .10)	.030

Data are means ± SD.

^aIndicates intergroup P values at the end of the study.

as the physical functioning subscale. The psychosocial health summary score (15 items) is computed as the sum of the items divided by the number of items answered in the emotional, social, and school functioning subscales.

Statistics

The study was designed to detect a clinically meaningful change of 25% in GHb levels with an SD of 0.75; for independent groups, the necessary sample size was 60 patients (30 patients in each arm). The interim analysis was done after 30 patients completed the study, and enrollment was stopped at that time since $P < .03$; however, patients who were enrolled but had not completed the protocol were allowed to continue the study.

Prism version 4 (GraphPad Software Inc, San Diego, CA) was used to generate graphs, whereas statistical analyses were performed with the advanced model of SPSS 13.0 (SPSS Inc, Chicago, IL). The data are expressed as means ± SD unless otherwise indicated. Significance was considered at $P < .05$ and confidence intervals at 95%. Data were analyzed for all patients with an intention-to-treat analysis. No ancillary analyses were performed.

Within-group changes in the parameters studied were analyzed using paired samples *t* tests, and between-groups data were analyzed by using independent samples *t* tests.

RESULTS

Patients

The study was conducted from February 2005 through mid-December 2006. Forty-two patients with new-onset type 1 diabetes were consented and randomly assigned. One patient rescinded consent citing no reason, and 5 patients were dropped from the study because of non-compliance to protocol. Thirty-one white, 3 black, and 2 Latino patients completed the study. Data from 19 patients (10 male, 9 female) in the IG group and 17 patients (8 male, 9 female) in the NPH group were analyzed.

Baseline Characteristics

Baseline characteristics did not differ significantly in the 2 treatment groups (Table 1).

GHb Levels

The primary analysis was intention-to-treat and involved all 42 patients who were randomly assigned at the 3-month visit. Three patients were excluded at 3 months when they failed to come in for a return visit at 3 months. One patient was lost to follow-up after consenting; she moved away from home after turning 18.

One patient decided to withdraw at the 3-month visit when randomization would have occurred. No reason was cited. Consequently, 36 patients remained for analyses per protocol. GHb levels at the end of the 3-month study period were statistically lower in IG plus RAI (19 of 36) versus NPH plus RAI (17 of 36) arms at 6.7 ± 1.3 vs 7.6 ± 1 ($P < .029$; Fig 2).

BG Levels

FBG Levels

The group that was receiving IG (16 of 28) had a significantly lower FBG (5.7 ± 2 mmol/L) than those who were receiving standard therapy (9.6 ± 5.1 mmol/L) at the end of the study ($P < .008$); the study arm showed a negligible decrease in FBG levels down from 6.6 ± 1.7 to 6 ± 1.4 mmol/dL ($P < .2$), whereas those on standard therapy (12 of 28) had significantly increased FBG levels up from 7.2 ± 1.3 to 10.4 ± 4.5 mmol/L ($P < .02$).

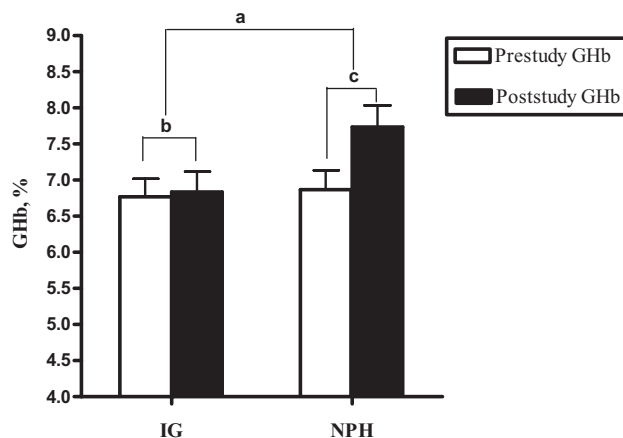


FIGURE 2

GHb in the study cohort. ^a $P < .029$; ^b $P < .7$; ^c $P < .049$.

TABLE 2 Insulin Dosage Percentages, Morning and Evening, in the 2 Study Arms

Parameter	Morning		Evening	
	LAI	RAIA	LAI	RAIA
IG arm (n = 19)	38.6 ± 11.7	20.0 ± 9.2	19.8 ± 9.0	15.3 ± 5.9
NPH arm (n = 17)	43.5 ± 9.6	18.7 ± 5.9	22.7 ± 7.2	15.0 ± 4.4
P	<.2	<.6	<.3	<.9

LAI indicates long-acting insulin.

LBG Levels

Poststudy versus prestudy, the patients who were taking IG (17 of 30) showed improved BG levels (8.3 ± 4.6 vs 7.2 ± 3.4 mmol/L), but this decrease was statistically insignificant ($P < .3$); the NPH arm (13 of 30) showed an insignificant deterioration (8.0 ± 2.7 vs 8.7 ± 4.9 mmol/L; $P < .6$).

SBG Levels

Mean SBG values in the glargine (17 of 30) versus NPH (13 of 30) arms prestudy were 7.1 ± 2.5 vs 7.9 ± 3.5 mmol/L ($P < .5$) and poststudy were 10.4 ± 4.9 vs 10.4 ± 5.9 mmol/L ($P < .1$).

Insulin Dosage

All 36 patients complied with their respective regimens and dosage changes, made only by the PI, during the course of the study. Insulin dosages were calculated per unit body weight. By the end of the study, there was an insignificant increase in insulin requirement in patients who were taking IG (19 of 36) from 0.5 to 0.75 U/kg ($P < .4$), whereas those who were receiving standard therapy (17 of 36) required significantly lower dosages, decreasing from 0.76 to 0.55 U/kg ($P < .05$). Despite these changes in insulin requirement, the difference in dosages between the 2 arms at the end of the study was not significant ($P < .5$). FBG and SBG levels were significantly different in the IG versus NPH arms; however, the LBG measurements were not significantly different (Table 1).

Table 2 describes the percentages of long and rapid-acting analog for the morning and evening doses. Although not statistically significant, it is interesting that the patients were on higher NPH morning and evening requirements compared with IG, but the RAIA requirements were no different between groups.

Body Mass Index

BMI in the IG (19 of 36) group decreased by 0.4 kg/m² ($P < .6$) but increased in the NPH group (17 of 36) by 0.8 kg/m² ($P < .01$). There was no significant difference between the treatment groups at either the start ($P < .5$) or the end ($P < .9$) of the study.

Hypoglycemia

There were no incidents of hypoglycemia seen in the IG group, but records indicate that 3 of the patients who were receiving standard therapy experienced 1, 2, and 4 episodes individually, not requiring hospital admission.

None of these 3 patients or any in the IG group self-treated for hypoglycemia on the basis of symptoms alone.

Contact With Health Care Provider

Two patients in the NPH group contacted the PI 1 time by telephone. In the IG group, 10 patients contacted the PI by telephone or e-mail and 7 of those had only 1 contact. Three of the patients in the IG group who contacted the PI >2 times called 14, 4, and 5 times during the study period requesting help with dosage adjustments. Reanalysis after exclusion of data that were obtained from these 3 patients in the IG arm who called most frequently continued to yield a significantly different GHb level in IG versus NPH: 6.8 ± 1.4 vs $7.6 \pm 1\%$ ($P < .05$).

Quality of Life

There was no significant difference in the QoL of the patients and their parents in both study arms.

Adverse Effects

No significant adverse events or effects were encountered in either treatment arm for the duration of the study.

DISCUSSION

In this study, we demonstrated that IG given twice daily, mixed with an RAIA in the same syringe, afforded better glycemic control than standard therapy during a 3-month period. Importantly, we encountered no adverse events when the patient mixed IG and an RAIA in the same syringe before self-administration, as demonstrated in our previous study,¹³ albeit contrary to the manufacturer's instructions. Furthermore, this is one of the largest prospective pediatric randomized studies using IG in pediatric type 1 diabetes; children as young as 6 years were included in the study.

Patients with new-onset type 1 diabetes were chosen to conduct this study because additional injections for lunch are usually not necessary during the first 6 to 9 months of treatment as a result of endogenous insulin secretion. Furthermore, a fair comparison with NPH was set up wherein no lunch injections are necessary because NPH should ideally cover for lunch-related carbohydrate intake. It is interesting that only 2 patients reported BG levels that were high at dinnertime and could not be corrected with increasing IG dosage in the morning and hence required the lunch injection. This however did not affect the statistical difference seen and allows clinicians to add that lunch injection as the patient exits the honeymoon phase.

A multicenter, randomized, single-blinded study of 125 adults with type 1 diabetes reported that IG was superior to NPH in improving GHb and FBG levels during intensive insulin therapy.²⁰ Another randomized, crossover study of 28 adolescents with type 1 diabetes showed that combination therapy with IG and Lispro was at least as effective as NPH insulin plus regular human insulin in maintaining glycemic control in ado-

lescents who were taking multiple daily injections.²¹ Surprisingly, an open-labeled, randomized study of 619 adults who were taking either bedtime IG or once/twice-daily NPH insulin, with both groups taking preprandial RAI, yielded significantly lowered FBG levels in the IG arm with no difference between the groups with respect to change in GHb levels.²² This finding of significantly lowered FBG levels in the IG arm is in concurrence with that of our study, but we concomitantly found significantly higher GHb levels in the NPH arm.

Split-dose IG versus morning/evening-dose IG was studied and resulted in no real advantage in glycemic control,²³ but these findings were not compared with standard therapy using NPH. In adolescents with type 1 diabetes, IG was found not only to be as effective as NPH in maintaining glycemic control but also to reduce the incidence of nocturnal hypoglycemia. In our study, hypoglycemia occurred more in the NPH arm, but neither group reported nocturnal hypoglycemia. In all studies^{24–29} except one,¹⁵ IG was given as a separate injection from the RAI, increasing the total number of daily injections. A retrospective chart review by Fiallo-Scharer et al¹⁵ demonstrated that there was no significant difference in mixing insulin glargine versus giving as a separate injection. This study is in agreement with our previously¹³ and currently reported findings.

In children, increasing the number of injections may adversely affect adherence to medication regimens, resulting in no improvement of glycemic control. This is further corroborated by a 3-year international survey of 2873 children and adolescents by the Hvidovre study group, which reported that metabolic control was not improved by the use of regimens of multiple insulin injection.³⁰ Similar results were also seen in a Danish study of 429 children during a 2-year period in which metabolic control deteriorated despite an increase in the use of multiple injection regimens from 39% to 54%.³¹ In our clinical practice, as also previously stated,⁴ most parents and patients are reluctant to take extra injections, limiting the use of IG. Our investigation is strongly suggestive that IG is as user-friendly as NPH with the added advantage of improved glycemic control, with the caveat that this will most likely apply only during the honeymoon phase of diabetes and that eventually a lunch injection will be necessary to achieve optimal glycemic control.

The limitations of our study are as follows: in hindsight, equal contact with both groups in a fixed, predetermined manner would have been better. Regardless, analysis of the data without the patients who called frequently in the IG group showed that IG was still superior to NPH at the end of the study. Moreover, because the PI was not blinded to the treatment arm of the patients, there is potential for bias that could affect the outcome in patients who contacted the PI. Another limitation of this study is its short duration; therefore, the differences seen at 6 months may not persist at 9 and 12 months.³²

The importance of lowering the GHb level is well established¹ and cannot be overstated, but GHb percentages were found to be inversely proportional to the rate

of hypoglycemic episodes.³³ Furthermore, in the DCCT, patients who were receiving intensive insulin management had a threefold increase in severe hypoglycemic episodes compared with patients who were receiving standard therapy.¹ IG elicits less hypoglycemia, especially nocturnal episodes, than NPH insulin but with comparable glycemic control.³⁴ Most studies reported a decrease in the severity and/or the number of nocturnal hypoglycemic episodes^{20,21,23,24,27,28}; one reported the occurrence of nocturnal hypoglycemia in significantly fewer patients,²⁹ and another reported no increase in severe hypoglycemic episodes when comparing patients who were receiving various IG regimens.²³

CONCLUSIONS

We have demonstrated that mixing IG with an RAI in the same syringe and giving it twice daily improves glycemic control as compared with standard therapy with NPH. Improving glycemic control without concomitant increases in the number of daily injections is pertinent to maintaining/improving compliance in the pediatric population. Moreover, hypoglycemic episodes were not different between the 2 groups. This study paves the way for incorporating intensive insulin management in type 1 diabetes with decrease in pain and burden of injections.

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