Preliminary Data of Insulin Glargine Use among Thai Adolescents and Young Adults with Type 1 Diabetes Mellitus Treated at Siriraj Hospital

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Insulin glargine is a new long-acting insulin analog with a duration of action of 24 hours and can be given once a day as the only basal insulin combined with short or rapid-acting insulin as bolus insulin for each meal.

The goals of this study were to evaluate short term result of treatment with insulin glargine compared to NPH and to determine the initial dosage of insulin glargine in Thai adolescents with type 1 diabetes.

We reviewed charts of 10 adolescents (median age 20.8 years, range 12.3-22.7 years) with type 1 diabetes who had received insulin glargine for ≥ 4 months (median 16.5 months, range 4-25 months). Before switching to insulin glargine, all patients received NPH. Seventy percent of subjects had improvement of HbA_{1c} from 10.4% (range 8.2-12.6) to 8% (range 6.7-10.6). The total amount of insulin dosage was significantly decreased from 1.2 (range 0.9-2.4) to 0.9 (range 0.4-1.5) units/kg/day as well as the percentage of basal insulin which was decreased from 70% (range 67-81) to 47% (range 38-56) of the total daily insulin. Insulin glargine did not cause severe hypoglycemia in this study.

Conclusion: *Insulin glargine is another promising therapy for adolescents with type 1 diabetes. We recommend the starting total daily insulin dosage to be decreased to 70-80% of previous dosage. Insulin glargine should be started at 50 % of the new total daily insulin dosage.*

Keywords: *Insulin glargine, NPH, Type 1 diabetes mellitus, HbA_{1c}*

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The Diabetes Control and Complications Trial (DCCT) clearly demonstrates that better glycemic control decreases risks of microvascular complications in patients with type 1 diabetes[1]. However, intensive glycemic control increases the frequency of hypoglycemic episodes[2]. Therefore, the optimal treatment of T1DM has always been a challenge for patients, their families and health care teams.

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Adolescents have extremely variable insulin requirements influenced by pubertal changes, lifestyle and mood changes[3]. A cross-sectional multinational study showed that less than one-third of children and adolescents with type 1 diabetes had adequate metabolic control[4]. The average HbA_{1c} in children with type 1 diabetes less than 18 years old from Asia-Pacific region was 8.7±1.9% while Thai children and adolescents with type 1 diabetes had the average HbA_{1c} of 8.8±2.3% [5]. Both of which were not satisfactory. Adolescents aged 15 to 18 years had the worst glycemic control among those children.

Most of the patients in our DM clinic are on conventional insulin regimen (twice daily injection with NPH and regular insulin). NPH insulin has a large

variability in duration of action and does not provide a 24-hour basal insulin supply. It also has a significant peak resulting in nocturnal hypoglycemia when given before dinner or at bedtime.

Insulin glargine, a new long-acting insulin analog was introduced into Thailand in 2003. It was approved by the US FDA in 2000 for the use in patients age $\geq$ 6 years with type 1 and type 2 diabetes. Insulin glargine precipitates when injected subcutaneously leading to delayed absorption and prolonged duration of action up to 24 hours. Insulin glargine cannot be mixed with other short or rapid-acting insulin. It can be given once a day as the only basal insulin along with short or rapid-acting insulin as bolus insulin for each meal[6].

The goals of this retrospective study were to determine the dosage of insulin glargine used as basal insulin among Thai adolescents and young adults with type 1 diabetes and to determine whether insulin glargine would improve glycemic control compared to NPH previously used in each individual.

Material and Method

We retrospectively reviewed the charts of 10 adolescents and young adults (3 males and 7 females) with type 1 diabetes who had received insulin glargine for at least 4 months during April 2003 to May 2005. A clinical decision was made to switch patients with poorly controlled diabetes, patients with frequent hypoglycemia and patients with brittle diabetes to insulin glargine in an effort to improve glycemic control.

Data of weight, height, body mass index (BMI), HbA_{1c} before initiating insulin glargine and at last clinic visits of all patients were collected. Insulin dosages were also collected at both time points. Episodes of admission, DKA and severe hypoglycemia during treatment with insulin glargine were recorded.

Patients were seen at 3-month interval. Starting dosages of insulin glargine, types and dosages of rapid-acting insulin (insulin aspart or humalog), dosage adjustment per carbohydrate exchange or blood sugar values were determined at each physician's discretion. Frequency of telephone contact to diabetes nurse educator or physician was at each patient's desire and at physician's discretion.

Severe hypoglycemia was defined as a hypoglycemic event resulting in unconsciousness, seizure, or a level of obtundation severe enough for patients to require assistance from another person. Since most of our patients monitored their blood glucose at home twice per day or less, the accurate frequency of asymptomatic or nocturnal hypoglycemic episodes before and after insulin glargine initiation were unavailable.

The differences between insulin dosages of the two groups were determined using Wilcoxon signed-rank test. Data are presented as median (range). The difference was statistically significant if p value was less than 0.05. However, the number of our subjects was too small to compare HbA_{1c} values and BMI between the two groups.

Results

Median age of subjects was 20.8 (range 12.3-22.7) years. Median duration of type 1 diabetes was 10.3 (range 3.7-13.2) years. Median duration of insulin glargine use was 16.5 (range 4-25) months.

Prior to switching treatment to insulin glargine, six patients received NPH and regular insulin or premixed insulin twice a day, three patients received NPH and regular insulin three times a day, and one patient received NPH and Humalog, a rapid-acting insulin three injections a day.

Two patients developed diabetic nephropathy prior to initiation of insulin glargine (at 5 and 6.5 years after their diagnosis of type 1 diabetes).

After switching to insulin glargine, 9 patients received insulin glargine at bedtime and one patient received insulin glargine before breakfast. All patients received rapid-acting insulin (Insulin Aspart in 9 patients, Humalog in 1 patient) as bolus insulin for each meal. The patients were not uniformly asked to adjust insulin glargine dosage according to their fasting blood glucose levels or to call the diabetic health care team on a fixed-time schedule.

Insulin glargine was well tolerated. There were no reactions at injection sites among our patients. No episode of severe hypoglycemia was noted.

Improvement of HbA_{1c} was seen in seven subjects (70%). Their HbA_{1c} dropped from 10.4% (range 8.2-12.6) to 8% (range 6.7-10.6). Three patients (30%) had worsening of their HbA_{1c} values (9.9 % (range 7.9-11.2) vs. 12.3 % (range 8.3-12.4)). Among these 3 patients, one had lost to follow up and the other 2 patients had been on insulin glargine for less than 6 months (5 and 5.5 months).

During insulin glargine treatment, 7 patients (70%) required less total daily insulin doses calculated in units/kg/day (75$\pm$27% of previous total daily insulin doses). Two patients required more insulin doses and one required the same total daily insulin dosage.

Table 1. Insulin dosage, BMI and HbA1c before and after treatment with insulin glargine

	Baseline	After insulin glargine	p value
BMI (kg/m^2)	23.3 (17.9-24.2)	22.1 (18.4-23.4)	0.2
HbA_{1c} (%)	10.4 (7.9-12.6)	8.6 (6.7-12.4)	0.1
Total insulin dosage (units/kg/day)	1.2 (0.9-2.4)	0.9 (0.4-1.5)*	0.03
Basal insulin dosage (% of total daily dosage)	70 (67-81)	47 (38-56)*	0.01

Data are presented as median (min, max)
$p < 0.05$= statistically significant

One 19 year-old girl with poor glycemic control (HbA_{1c} =12.6%) and history of multiple DKA episodes developed 2 episodes of DKA at 2 and 10 months after switching to insulin glargine (HbA_{1c} 12.7% and 13.9% respectively). However, her HbA_{1c} improved after 16 months of treatment with insulin glargine to 10.6%.

Discussion

In the present study, insulin glargine was at least equally as effective as NPH in controlling type 1 diabetes in adolescents and young adults. Insulin glargine improved glycemic control in the majority of our patients. Meanwhile, insulin glargine did not cause severe hypoglycemia in this study. The requirement of total daily insulin dosage was less (75 % of previous dosage) during treatment with insulin glargine. The percentage of insulin glargine was approximately 50% of total daily insulin dosage.

Although our study did not allow us to compare the difference of HbA_{1c} before and after treatment with insulin glargine due to the small number of subjects, the majority of our patients had improvement of their glycemic control after switching to insulin glargine. More subjects are needed to detect the difference in HbA_{1c}. We plan to further evaluate the glycemic control in larger numbers of children and adolescents with type 1 diabetes treated with insulin glargine in our DM clinic.

Previous studies demonstrated that there was no significant difference in HbA_{1c} between children treated with insulin glargine and children treated with NPH insulin[7, 8]. However, other study reported that 6 months duration of insulin glargine improved HbA_{1c} in adolescents with poorly controlled type 1 diabetes[9]. The conflicting results among these studies could be due to difference in frequency of patients' contact with health care team, titration methods and their baseline HbA_{1c}.

Previous data have shown that insulin aspart significantly improved postprandial blood sugar compared to regular insulin[10]. Therefore, it is worth to note that the observed HbA_{1c} after treatment with insulin glargine reflected the efficacy of both insulin glargine and insulin aspart, not insulin glargine alone.

Regarding the starting doses of insulin glargine, we recommend that the total insulin dosage should be decreased to 70-80% of previous total daily insulin dosage. However, some adolescents especially those who have not completed their puberty may ultimately need more insulin dosage. We also recommend that insulin glargine dosage should be started at approximately 50 % of the total daily insulin dosage. We recommend frequent phone contacts between the patients and health care providers especially during the active titration periods of insulin glargine since the initial starting doses could be suboptimal for some patients.

Insulin glargine did not cause severe hypoglycemia among our patients. However, our study did not allow us to evaluate the frequency of nocturnal or asympmatic hypoglycemic episode since the patients checked their blood glucose at their own desire and frequencies of their home blood glucose monitoring were inadequate. Previous data have shown that insulin glargine reduced the frequency of nocturnal and severe hypoglycemic episodes in children with type1 diabetes compared with NPH [11-13].

Disadvantage of insulin glargine is that patients have to receive more injections compared to NPH, since insulin glargine cannot be mixed with other types of insulin and does not provide a peak effect. Young children who would need supervision to receive an insulin injection at school could give insulin glargine before dinner or at bedtime combined with NPH insulin in the morning[8]. NPH will peak around noon thus patients can avoid noon insulin injection for lunch.

In conclusion, insulin glargine is at least as effective as NPH in the treatment of adolescents and young adults with T1DM. Insulin glargine improved glycemic control in 70% of our patients. It provides more flexible lifestyles as compared to NPH. Therefore, insulin glargine is another promising therapy for adolescents and young adults with T1DM. We recommend that the starting total daily insulin dosage should be decreased to 70% of previous total daily insulin dosage. Insulin glargine should be started at approximately 50 % of the new total daily insulin dosage. Frequent phone contact between the patients and health care providers is recommended especially during the active titration periods of insulin glargine.

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ผลเบื้องต้นของการใช้อินซูลินกลาจีนในเด็กวัยรุ่นไทยที่เป็นเบาหวานชนิดที่ 1 ที่ได้รับการรักษาที่โรงพยาบาลศิริราช

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อินซูลินกลาจีนเป็นอินซูลินชนิดใหม่ที่ออกฤทธิ์นาน 24 ชั่วโมง ผู้ป่วยเบาหวานชนิดที่ 1 สามารถฉีดอินซูลินกลาจีนเพียงวันละ 1 ครั้งเป็นอินซูลินพื้นฐาน โดยฉีดร่วมกับอินซูลินที่ออกฤทธิ์สั้นสำหรับมื้ออาหารแต่ละมื้อ

จุดประสงค์: *เพื่อประเมินผลในการรักษาระยะสั้น ในผู้ป่วยวัยรุ่นที่เป็นเบาหวานชนิดที่ 1 เมื่อฉีดอินซูลินกลาจีนโดยเปรียบเทียบกับ NPH และหาปริมาณอินซูลินเริ่มต้นที่เหมาะสม*

การศึกษาเป็นการเก็บข้อมูลจากแฟ้มผู้ป่วยเบาหวานชนิดที่ 1 จำนวน 10 คน (ค่ามัธยฐานของอายุ 20.8 ปี, ค่าพิสัย 12.3-22.7 ปี) ที่ฉีดอินซูลินกลาจีนเป็นเวลา $\geq$ 4 เดือน (ค่ามัธยฐาน 16.5 เดือน, ค่าพิสัย 4-25 เดือน) ก่อนที่จะเปลี่ยนมาฉีดอินซูลินผู้ป่วยทั้งหมดฉีด NPH ผู้ป่วย 70% มีระดับ HbA_{1c} ลดลงจาก 10.4% (ค่าพิสัย 8.2-12.6%) เป็น 8% (ค่าพิสัย 6.7-10.6%) ปริมาณอินซูลินที่ใช้ต่อน้ำหนักตัวลดลงในแต่ละวันอย่างมีนัยสำคัญทางสถิติจาก 1.2 (ค่าพิสัย 0.9-2.4) เป็น 0.9 (ค่าพิสัย 0.4-1.5) ยูนิต/กก./วัน รวมไปถึงปริมาณอินซูลินพื้นฐานที่ลดลงจากร้อยละ 70% (ค่าพิสัย 67-81) เป็น 47% (ค่าพิสัย 38-56) ของปริมาณอินซูลินที่ใช้ในแต่ละวัน และไม่พบภาวะน้ำตาลต่ำอย่างรุนแรงในการศึกษานี้

สรุป: *อินซูลินกลาจีนเป็นอีกทางเลือกหนึ่งของการรักษาเบาหวานชนิดที่ 1 ในวัยรุ่น เมื่อเปลี่ยนมาฉีดอินซูลินกลาจีนควรลดขนาดของอินซูลินรวมต่อวันเหลือ 70 - 80% ของขนาดเดิม และคำนวณให้อินซูลินกลาจีนเป็น 50% ของอินซูลินรวมต่อวัน*