

# Evaluation of the Efficacy and Safety of Once Daily Injection of Glargine Combined with Glipizide GITS in the Treatment of Type 2 Diabetes Mellitus

BU Shi, XING Xiao-yan, WANG Na, ZHAO Wen-hui, YANG Wen-ying ( Department of Endocrinology, China-Japan Friendship Hospital, Beijing 100029, China. )

## Abstract

**Objective:** To compare the blood glucose level and associated hypoglycemia risks by using insulin Glargine or human NPH both combined with Glipizide GITS in the treatment of type 2 diabetic patients.

**Methods:** Fifty-six cases with inadequate glycemia control by sulfonylurea and/or other oral agents were randomized in two groups (31). In the Glargine group, 42 patients were given Glipizide GITS 5 mg every morning and injection of Glargine at bedtime daily, while 14 patients in the NPH group were given Glipizide GITS 5 mg every morning and injection of NPH at bedtime daily. The dosage of insulin was adjusted by FBG level, seeking a target of FBG < 67 mmol/L, and the treatment lasted for 12 weeks. The blood glucose level and incidence of hypoglycemia were observed. The daily dosages of Glargine and NPH were recorded to analyze their relations between FBG and BMI at the beginning of the trial.

**Results:** Mean of FBG and daily glucose profile were similar in the 2 groups, but the incidence of hypoglycemia in the Glargine group was significantly lower than that in the NPH group (3 cases in the Glargine group, 7.1%, 5 cases in the NPH group, 35.7%,  $\chi^2 = 7.0$ ,  $P = 0.008$ ). Mean daily dosages of glargine at the end point were closely related to FBG and BMI at baseline.

**Conclusions:** Bedtime injection of Glargine combined with Glipizide GITS can achieve target blood glucose control and is safer than NPH. This simple "one pill-one injection" regimen may help us achieve recommended blood glucose control targets with better patients' compliance.

**Keywords:** Glargine, Glipizide, Type 2 diabetes mellitus, Randomise controlled trial.

DCCT, UKPDS and some other evidence-based medicine studies have led people to a consensus on the significance of target blood glucose control that can not only prevent or delay the incidence of chronic diabetic complications, improve patients' quality of life but also considerably reduce the medical costs relating to diabetes. Alc <7% can significantly reduce the risk of microvascular complication with diabetes mellitus. However, as a matter of fact the target blood glucose control rate is very low among diabetic patients. It is reported in a statistical result that about two-thirds of diabetic patients under treatment have not reached the therapeutic objective. With lengthening of the duration of type 2 diabetes mellitus, most patients cannot achieve the strengthened efficacy by oral hyperglycemic agents only. So insulin therapy becomes an important way to realize target blood glucose control.

What people concern is when to start insulin therapy and what therapeutic schedule is appropriate. Here, we adopt the schedule of insulin Glargine or human NPH both combined with Glipizide GITS to treat type 2 diabetic patients and seek a target of FBG <67mmol/L, simultaneously observing the blood glucose level and incidence of hypoglycemia and recording the daily dosages of insulin Glargine to analyze its relationships with FBG, BMI and duration of disease when FBG reaches the blood glucose control target in order to provide some references to the clinical application of insulin Glargine.

## 1. Object and Methods

This trial adopts an open, masculine, parallel and randomized comparison method. The candidate insulin Glargine was manufactured by Gan & Lee Pharmaceutical in the specification of 100 IU/m and

10ml/bottle. Neutral protamine hagedorn Biosynthetic Human Insulin Injection-Novolin N was manufactured by Danish Novo Nordisk A/S in the specification of 100 IU/ml and 3ml/bottle. Glipizide GITS (Ruiyining) was manufactured Pfizer in the specification of 5mg per tablet.

### **1.1: Object**

**1.1.1: Case Selection:** All cases came from type 2 diabetic patients who received medical diagnosis in our hospital and had case history of more than 1 year. Inclusion criteria: (1) inadequate glycemia control by using oral hyperglycemic agents (sulfonylurea combined with other oral agents) for 3 months at least, the dosage of previously-used sulfonylurea and the like was at least equal to 75mg glibenclamide; (2) aged 35~75; (3) BMI 19~30 kg/m<sup>2</sup>; (4) 7.0 mmol/L **1.1.2: Grouping:** Include screening period, 2 weeks' inclusion period and 12 weeks' treatment period. The eligible candidate objects took 5mg Ruiyining every morning instead of original oral hyperglycemic agents in the inclusion period, and 3 weeks later were randomized at 3:1 ratio into insulin Glargine group and NPH group in the order of inclusion time. Both groups received subcutaneous injection of insulin Glargine or NPH at 10pm, without stopping taking 5mg Ruiyining every day.

### **1.2: Methods**

**1.2.1: Treatment information:** Both groups patients received subcutaneous injection of insulin Glargine or NPH at 10pm every day and orally took 5mg Ruiyining every morning. Insulin dosage adjustment: firstly 1.5 IU/(kg·d), then increased by 2 IU every 3d until FBG <6.7mmol/L or subject to objects' actual conditions. Use Johnson & Johnson's onetouch ultra meter to measure daily FBG through collecting the fingertip blood of patients in the treatment period, and monitor the blood glucose at 8 time points every day after treatment for 0, 8, 12 weeks (including blood glucose levels before breakfast, lunch and dinner, 2h after meal, fingertip blood glucose). Technical trainings on injection and blood glucose measurements were provided to the objects before the first injection of insulin. Objects were required to record any and all adverse events in the treatment period. The blood glucose level lower than 4.0 mmol/L was defined as hypoglycemia. If hypoglycemia occurred, measure the level of blood glucose before the meal in order to release the situation.

After the end of screening period and 12 weeks' treatment, examine urine, urine routine, hepatic and renal functions, blood fat and ECG, which results were used as safety evaluation indexes.

**1.2.2: Statistical analysis:** Use SPSS 10.0 statistical software to analyze all data.  $c \pm S$  was used to express normal distribution variables. The paired t was used to compare FBG, postprandial and Alc, independent t was used to compare the baseline and the variables in two groups after the treatment.  $c^2$  was used to compare the numbers of hypoglycemia in two groups.

## **2. Results**

Total 56 cases were randomized into insulin Glargine group (42 cases) and NPH group (14 cases) and all received clinical observation for 12 weeks. The withdrawal rate was zero and the patient's compliance was good.

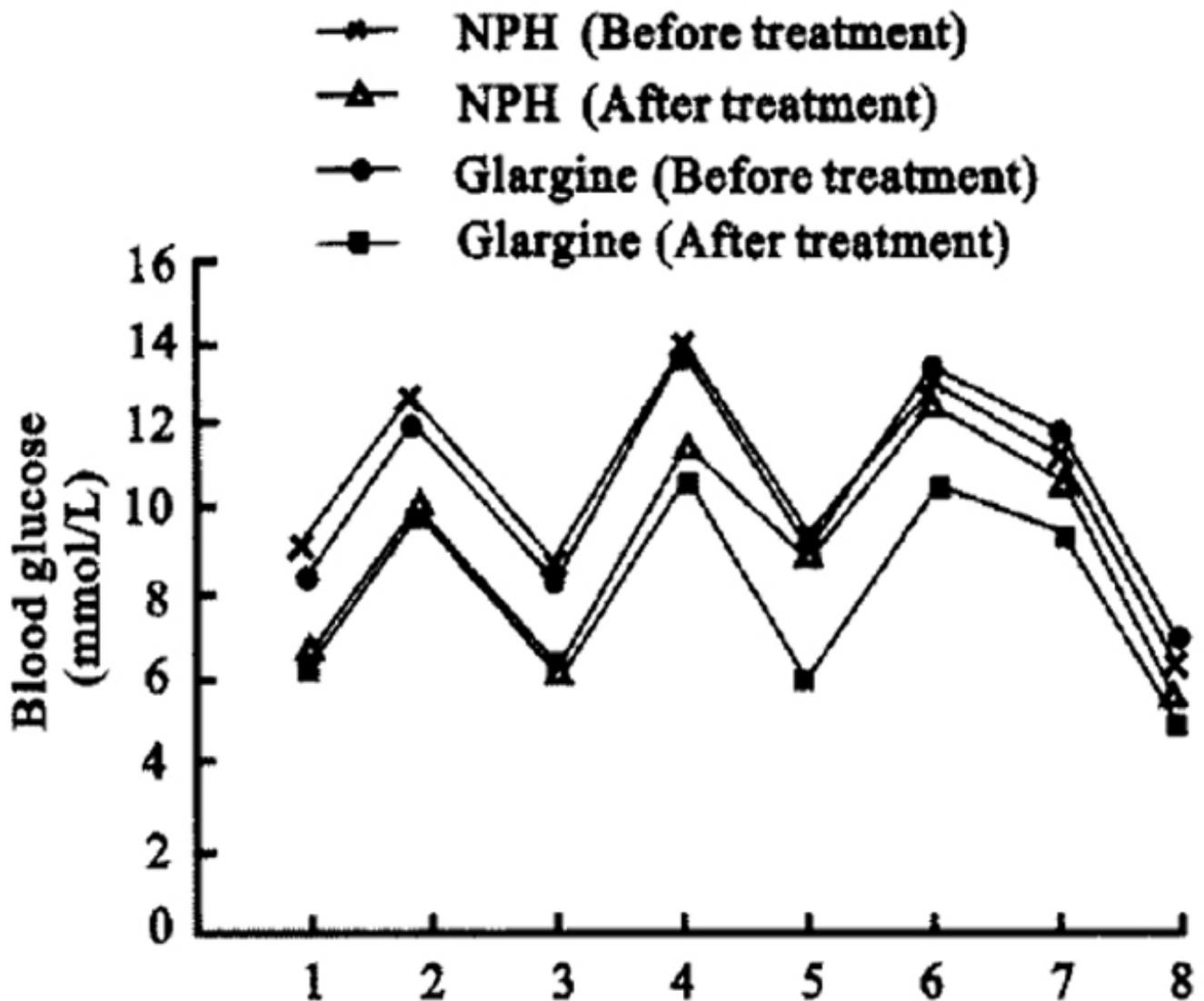
### **2.1: Baseline characteristics of subjects in the study**

**Table-1:** Baseline Characteristics of Subjects in the Study.

	<b>Glargine</b> <b>(n = 42)</b>	<b>N P H</b> <b>(n = 14)</b>
Gender (F/M)	20/22	10/4
Age (Year)	60.13±7.14	62.15±5.16
Duration (Year)	7.13±3.13	7.11±4.11
Alc (%)	8.12±2.19	8.18±3.10
BMI (kg/m <sup>2</sup> )	23.17±2.19	25.10±3.10
FBG (mmol/L)	8.14±2.12	9.11±2.17
<b>Prior therapy</b>		
SU + metformin	28 (66.7 %)	10 (71%)
SU only	12 (28.6 %)	4 (29%)
SU + Metformin + Acarbose	2 (4.17%)	0 (0%)

See Table-1 for the clinical comparison of the objects in two groups, both were similar in the age, duration of diabetes mellitus, FBG, combined drugs and hepatic and renal functions, except the gender.

## **2.2 Efficacy comparison**



**Figure:** 8-Point Blood Glucose Profile before And after 12w Treatment.

Note: 1. Fasting; 2. After breakfast ; 3. Before lunch; 4. After lunch; 5. Before dinner; 6. After dinner; 7. Before bed; 8. 3 am.

2.2.1 See the figure below for the change of blood glucose profile in two groups before and after treatment. There was no significant difference in blood glucose profile between two groups before and after treatment, similarly the decrease of the level of blood glucose after the treatment. However, at the end-point of treatment, 8-point blood glucose level in insulin Glargine group was lower than that of NPH group, particularly the values before and after the dinner. The average values of BG before dinner were  $6.8 \pm 2.2$  mmol/L and  $8.9 \pm 3.5$  mmol/L ( $P = 0.011$ ), respectively, and after dinner,  $10.8 \pm 3.2$  mmol/L and  $12.6 \pm 2.8$  mmol/L ( $P = 0.069$ ), respectively.

There was no significant difference between insulin Glargine group and NPH group in A1c decrease (respectively 0.82% and 1.1%,  $P = 0.244$ ).

### 2.3 Hypoglycemia comparison of objects in two groups

**Numbers of objects having hypoglycemia in the treatment:** 3 objects in insulin Glargine group (7.1%), 5 objects in NPH group (35.7%). The incidence rate of hypoglycemia in insulin Glargine group was significantly lower than NPH group ( $x^2=7.0$ ,  $P=0.008$ ).

### 2.4 Relation of mean daily dosages of Glargine and baseline FBG and duration of diabetes when

## achieved target FBG

**Table 2:** The relation of mean daily dosages of Glargine and baseline FBG, BMI, duration of diabetes when achieved target FBG.

FBG			BMI			Duration		
n	Baseline (mmol/L)	Glargine dose [IU/(kg d)]	n	Baseline (kg/m <sup>2</sup> )	Glargine dose [IU/(kg d)]	n	Duration (years)	Glargine dose [IU/(kg d)]
14	<7.6	0.18 ± 0.04	20	<23	0.19 ± 0.05	18	<7	0.24 ± 0.11
14	7.6-8.7	0.22 ± 0.05	22	≥23	0.18 ± 0.04	24	≥7	0.26 ± 0.18
14	>8.7	0.36 ± 0.22						

See Table 2. Divided objects in insulin Glargine into 3 subgroups according to the baseline FBG and calculated the daily dosage of Glargine when achieved target FBG. There was significant difference between the subgroups which baseline FBG < 7.6 mmol/L and baseline FBG >8.7mmol/L in the daily dosage of Glargine (P=0.021). Divided objects in insulin Glargine into 2 subgroups according to the baseline BMI and calculated the daily dosage of Glargine when achieved target FBG. There was significant difference between the subgroups which baseline BMI<23 kg/m<sup>2</sup> and baseline BMI >23 kg/m<sup>2</sup> in the daily dosage of Glargine (P=0.019). Divided objects in insulin Glargine into 2 subgroups according to the duration of diabetes and calculated the daily dosage of Glargine when achieved target FBG. There was no significant difference between 2 subgroups.

### 3. Discussion

There had been international and domestic multi-centers' reports on the efficacy and safety of ultra-long-acting insulin Glargine and NPH. This trial also proved that both had similar effect in reducing A1c level when achieved target FBG and that insulin Glargine had lower hypoglycemia rate than NPH, i.e., insulin Glargine had higher safety than NPH when achieved same target blood glucose control. At the trial endpoint, 8-point blood glucose levels in insulin Glargine group were lower than those of NPH group. The blood glucose levels in insulin Glargine group before and after dinner had, or almost had, significant difference from those of NPH group, possibly because of the pharmacokinetics characteristic of insulin Glargine that it could maintain 24h stable blood concentration. This was one of the advantages of ultra-long-acting insulin Glargine, viz., to provide 24h basal insulin substitute. NPH's acting period was only 12~16 h, which might be the cause that it was hard to control blood glucose level after dinner by only one injection of NPH every day. In addition, such ultra-long-acting insulin Glargine that acted relatively stably could be injected at any fixed time, conveniently for the use by patient.

Upon this trial, once daily injection of insulin Glargine, plus oral hyperglycemic agents, could enable more diabetic patients reach the target of A1c<7 % in a safe way. This trial also gave an ideal example of blood glucose control by "once injection and one tablet every day", which not only reached target blood glucose control but remarkably reduce the incidence rate of hypoglycemia, simultaneously simplifying the insulin therapy of type 2 diabetes mellitus, improving patient's compliance and having diabetes mellitus controlled in an ideal, safe and convenient way. This schedule might be a good transition to complete insulin substitute in the future.

UKPDS's study revealed from the aspect of evidence-based medicine that type 2 diabetes mellitus was a progressive one. All patients would experience from high secretion to hyposecretion of insulin. In OGTT curve, the insulin area among the patients with FBG > 160 mg/dl was lower than the normal level, it was the physiological need to supplement insulin. Therefore, supplementary insulin therapy would be an effective way to maintain target blood glucose control and delay the progress of disease. In "the treat to target" study made by Ridlle, the average duration of diseases was 8.4 ±5.55 years, BMI was 32.5 ±4.64 kg/m<sup>2</sup>, type 2 diabetic patients with inadequate glycemia control by oral hyperglycemic agents (A1c 8.61 % ±0.9 %) were given insulin Glargine in addition to original oral hyperglycemic agent, and their average FBG was decreased from 11 mmol/L to 6.5 mmol/L 24w treatment. A1c of

60% of patients was lower than 7%. This showed that the sufficient basal supplementary insulin close to physiological secretion was necessary to reduce FBG and significant to ideally control the overall blood glucose level. The ultra-long-acting insulin Glargine was likely to conceptionally and strategically change the therapy of type 2 diabetes mellitus.

It was found in this trial that the daily dosage of insulin Glargine had significant relation with baseline FBG and BMI when achieved target FBG. This paper gave the reference daily dosage of insulin Glargine to have FBG to reach the target level at different levels of FGB and BMI, which could to some extent be a reference for the supplementary therapeutic schedule of insulin Glargine for type 2 diabetes mellitus. In "the treat to target" study, the daily dosage of insulin Glargine and neutral protamine hagedorn supplemented to reach the target of FBG <5.6 mmol/L was 0.42~0.48 IU/kg, possibly in relation to the fatty objects (BMI was about 32 kg/m<sup>2</sup>) and higher baseline FBG (about 11mmol/L). In this trial, Chinese objects' resistance to insulin was not as more as foreigners, 0.2~0.4 IU/kg daily dosage would be safe according to objects' body weight, FBG and duration of disease. It was safe and feasible for most objects in the dosage of 0.2 IU/kg firstly then increasing according to FBG. In addition, the duration of disease was significantly related to the islet function that had been proved in lots of past studies to be an important factor influencing the target blood glucose control. It was not found in this trial that the daily dosage of insulin Glargine was relevant to the duration of diabetes mellitus, possibly because of less sample cases and small number of objects with long case history.

It was hard to make refined analysis due to small quantity of research samples. Further study was needed with more research samples for the applicability of the schedule "once injection and one tablet every day".

## References

1. UKPDS Study Group 1 Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR1 Association of glycaemia with macrovascular and microvascular complications of Type 2 diabetes: prospective observational study (UKPDS 35) [J] 1 BMJ, 2000; 321 (12): 405-412.
2. UKPDS Study Group 1 Klein R, Klein BE, Moss SE1 Relation of glycemic control to diabetic microvascular complications in diabetes mellitus [J] 1 Ann Intern Med, 1996; 124 (1 Pt 2): 90-96.
3. Wright A, Burden ACF, Paisey RB1 Sulfonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U K Prospective Diabetes Study (U KPDS 57) [J] 1 Diabetes Care, 2002; 25 (2): 330-336.
4. HOE 901/3002 Study Group1 Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes [J] 1 Diabetes Care, 2000; 23 (8): 1130-1136.
5. Riddle MC, Rosenstock J, Gerich J1 Insulin Glargine 4002 Study Investigators1 The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients [J] 1 Diabetes Care, 2003; 26 (11): 3080-3086.
6. UKPDS Study Group 1 Overview of six years' therapy of type 2 diabetes a progressive disease (U KPDS 16) [J] 1 Diabetes Care, 1995; 44 (11): 1249-1258.
7. Turner RC, Cull CA, Frighi V, Holman RR1 Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus : progressive requirement for multiple therapies (UKPDS 49) 1 UK Prospective Diabetes Study (UKPDS) Group [J] 1 JAMA, 1999; 281 (21): 2005-2012.
8. Matthaie S. Endocrine review [M], 21 (6): 585-618.

## *Benefits of early insulinization*

- ✓ *Provides better glycemic control*
- ✓ *Delays the risk of development and progression of diabetes complications*
- ✓ *Improves quality of life*

# Every 1% reduction in HbA<sub>1c</sub> reduces diabetes complications

HbA<sub>1c</sub>  
1%

