Insulin Therapy and Blood Glucose Monitoring Evaluation of the Superiority of Glargine as Basal Insulin Replacement by Continuous Glucose Monitoring System

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Abstract

Summary: With the continuous glucose monitoring system, daily blood glucose profiles were compared in type 2 diabetic patients treated with glargine or neutral protamine hagedorn (NPH) at bedtime for 12 weeks. The blood glucose levels in these patients were previously not well controlled with sulfonylureas. The results suggested that combined treatment with glargine before bedtime showed less nocturnal hypoglycemia and more stable blood glucose profile with less exertion when fasting blood glucose levels were well controlled.
Keywords: Continuous glucose monitoring system, Diabetes mellitus, type 2, Glargine.

The recombinant human glargine insulin is a long-acting human insulin analog manufactured by using recombinant DNA technology and simulates basal islet secretion. Continuous glucose monitoring system (CGMS) can continuously monitor glucose variability for 24 hours to find inapparent nocturnal hypoglycemia and postprandial hyperglycemia that are always neglected by self-glucose monitoring. In this trial CCMS technology was used to observe the blood glucose profile and hypoglycemia of type 2 diabetes mellitus (DM) patients treated with sulfonylureas, plus glargine, for 12 weeks, in order to evaluate the superiority of glargine as basal insulin replacement compared with neutral protamine hagedorn (NPH).

I: Objects and Methods

1. Selection of objects: criteria of candidate objects in this trial: type 2 DM patient with history of over 6 months, aged 35~70, with blood glucose levels not well controlled with sufficient sulfonylureas (at least in the dosage of 7.5mg/d glibenclamide) only or combined with other oral hypoglycemic agents given for more than 3 months [7.0mmol/L < fasting blood glucose (FBG) < 13.0 mmol/L], without serious cardio-cerebral vascular diseases or obvious hepatic or renal function impairment. Totally 24 type 2 DM cases were included in this trial.

2. Methods: (1) Provided education on DM knowledge to the objects until they could take food according to the program made by the physician and skillfully use ONETOUCH Ultra (manufactured by Johnson); (2) Objects were given Glipizide GITS (Ruiyining, manufactured by Pfizer) 5 mg before breakfast for 2 weeks; chose 8 objects for CGMS examination at 2w treatment with Ruiyining; (3) Divided objects into 2 groups after 2w washout period, one group (16 cases) was given Ruiyining combined with once subcutaneous injection of glargine (recombinant glargine insulin injection manufactured by Gan & Lee Pharmaceutical) before bedtime; the other group (8 cases) was given Ruiyining combined with once subcutaneous injection of NPH (Novolin N) before bedtime. The initial dosage in two groups was 0.15 IU/kg/d and then increased or decreased by 2 IU every 3 days until daily FPG < 6.4 mmol/L. All objects received CGMS examination after 12w treatment; (4) Recorded the hypoglycemia information in the trial period, and measure blood glucose level and HbA1c in venous blood at the beginning and end of the trial.

3. See the literatures for the structure, composition and process of CGMS.

4. Laboratory examination: Measure blood glucose level by using hexokinase method, HbA1c by HPLC method, lot and inter-lot difference < 5%.

5. Statistical analysis: Used c ± S to express measurement data, paired t to compare the difference between before and after intra-class trial, variance analysis to compare the variance in two groups before and after trial, and frequency number (constituent ratio) to make statistical description of the enumeration data. Used c2 to monitor the variance in two groups before and after treatment, and Fisher when theoretical frequency < 5.

II: Results

1. General and laboratory data of objects: 24 type 2 DM patients were included in this trial. Eight cases were selected for CGMS examination, whose baseline data had no statistical significance when compared with that of the whole group, having good representative.

Table-1: General Date of Objects ($\bar{\chi} \pm S$).

Group	Treatment	n (F/M)	Age (Y)	Duration (Y)	BMI (kg/m^2)	FPG (mmol/L)	HbA$_{1c}$ (%)
Ruiyining		8(4/4)	56±7	9.9±5.3	24.3±2.9	10.45±1.8	8.79±1.09
NPH	Before	8(4/4)	56±8	9.5±4.9	24.6±2.5	10.40±1.5	8.75±1.24
	After	8(4/4)	-	-	24.9±2.3	5.84±1.26	7.43±0.73
Glargine	Before	16(9/7)	56±6	10.4±4.3	24.2±2.8	10.58±1.87	8.77±1.18
	After	16(9/7)	-	-	24.7±2.4	6.06±1.2	7.62±0.98

Note: NPH: neutral protamine hagedorn; BMI: body weight index; FPG: fasting blood glucose; comparison with index before treatment: *P < 0.05.

As shown in Table 1, all baseline data of glargine group and NPH group had good representative.

2. Efficacy of glargine in the treatment of type 2 DM patients: (1) Comparison of FPG and HbA1c before and after treatment: as shown in Table 1, after 12w treatment: the levels of FPG and HbA1c in both glargine group and NPH group were significantly decreased (P <0.05), the decrease difference between two groups had no statistical significance (P >0.05). (2) CGMS data comparison: A. General data: all objects didn't feel discomfort in CGMS examination and their daily life almost was not affected, without infection or inflammation at the sites of puncture. The monitoring time was (68.2±4.4) hours, CGMS recorded glucose data for (818±53) times. B. CGMS index comparison: after 12w treatment: a. with Ruiyining combined with NPH or glargine, the time percentage of average glucose level, standard deviation of glucose and blood glucose level >10.0mmol/L (TPG >10.0mmol/L %) were significantly decreased (P<0.05). b. at well-controlled and close FPG level, the glucose levels after lunch, before dinner and at 0am and 3am were significantly decreased (P<0.05); c. compared with NPH group, the glucose levels in glargine group before dinner and bedtime were more decreased (P<0.05), the glucose level at 3am was not too low (P<0.05), the decrease curve from injection before bedtime to the next morning was stable. (3) Comparison of incidence rate of hypoglycemia:

Table-2: Comparison of CGMS Indexes among Groups Ruiyining, NPH and Glargine after 12w Treatment ($\bar{\chi} \pm S$).

Group	n	Average blood glucose (mmol/L)	Standard glucose deviation (mmol/L)	Standard FPG deviation (mmol/L)	Standard glucose deviation before bedtime (mmol/L)	TPG ≥10.0 mmol/L (%)	Nocturnal TPG ≤3.0 mmol/L (%)
Ruiyining	8	11.3±3.1	3.1±0.6	2.2±0.4	3.3±1.0	62.4±15.5	0±0
NPH	8	8.0±2.0	2.3±0.5	1.5±0.7	2.0±0.7	23.9±11.7	5.88±1.96
Glargine	16	8.2±1.2	1.4±0.4	0.7±0.4	1.2±0.4	25.9±12.6	2.56±1.79

Group	n	Blood Glucose at Different Time Points (mmol/L)							
		Before breakfast	2h after breakfast	Before lunch	2h after lunch	Before dinner	2h after dinner	Before bedtime	3am
Ruiyining	8	8.5±2.2	13.5±3.4	8.0±1.5	13.5±2.0	8.5±0.9	12.7±2.4	10.9±3.3	8.4±1.7
NPH	8	5.8±1.5	10.4±1.9	6.6±1.2	10.2±1.8	7.1±1.0	11.7±1.4	9.2±2.0	4.2±1.4
Glargine	16	5.5±0.8	9.8±2.6	5.9±1.0	9.8±1.5	6.0±0.7	10.8±1.6	7.8±1.2	5.1±0.8

Note: CGMS: continuous glucose monitoring system; TPG: time percentage of blood glucose; abbreviation: same as Table 1; comparison with Ruiyining group: *P < 0.05; comparison with NPH group: *P < 0.05.

as shown in Table 2, the time percentage of nocturnal hypoglycemia <3.0 mmol/L (TPG <3.0mmol/L %) as recorded in CGMS examination (20:00~next 6:00) in the 12th week in glargine group was significantly lower than that of NPH group. CGMS examination in the 12th week showed that the

incidence rates of overall hypoglycemia were similar in two groups: 6 cases with 4 objects in NPH group and 2 cases with 2 objects in glargine group, but the nocturnal hypoglycemia rate in glargine group (1 case) was significantly lower than that of NPH group (4 cases). No serious hypoglycemia occurred in two groups.

III: Discussion

Generally in DM treatment, blood glucose monitoring was implemented with household blood glucose meter, which only measured the blood glucose level at one time point and couldn't find nocturnal inapparent hypoglycemia or display the duration of hyperglycemia after meal. CGMS could observe 24 glucose variance curve in the whole day including sleeping time without waking patient up. So this system could play a good role in monitoring blood glucose level and directing DM treatment.

The objective of basal insulin replacement was to maintain 24h insulin concentration close to physiological state and could control nocturnal hyperglycemia and morning status without increasing the risk of nocturnal hypoglycemia. Glargine was a long-acting insulin analog synthesized with genetic recombination technology, it could change the molecular structure and physiochemical property of insulin through modifying the types and numbers of amino acid molecule in insulin molecule. After subcutaneous injection, glargine could form micro-sedimentation to delay body absorption and so lengthened acting time and produced stable and longer action, consistent with physiological basal insulin secretion.

Before the development of glargine, the mostly-used method among basal insulin replacement schedules for DM patients was NPH subcutaneous injection before bedtime. NPH has a short acting time and reaches peak value 4~6h (about 3am) after being subcutaneously injected before bedtime, then significantly gets weak in the next morning. In order to reach target FPG control, it often needs to increase NPH dosage. This will increase the incidence rate of nocturnal hypoglycemia. Glargine is absorbed at a steady speed and has a moderate action without obvious peak time, so it will not lead to violent glucose variance. In this trial CGMS examination clearly showed that at close overall glucose levels, well-controlled and close FPG, glargine group had well-controlled glucose levels before dinner and bedtime, more stable 24h glucose curve, particular the decrease curve before bedtime to the next morning, without hypoglycemia at 3am and with low incidence rate of nocturnal hypoglycemia, further proving its high stability and providing great convenience to adjust the therapeutic schedule.

The decrease of glucose variance among DM patients receiving insulin therapy has important significance. According to the studies in recent years, glucose variance is also a risk factor leading to complication and bad prognosis, its hazard is even higher than pure hyperglycemia among some patients. In this trial, glargine was used as basal insulin replacement and significantly reduced the glucose variance among objects, mostly manifested by the significant decreases of standard glucose deviation, standard FPG deviation and standard glucose deviation before bedtime, showing glargine could maintain stable the level of insulin blood, well control nocturnal glucose level, better inhibit dawn phenomenon and reduce daily glucose variance. The decrease of standard FPG deviation indicated the good estimation of glargine; the decrease of standard glucose deviation before bedtime indicated the dosage of injection before bedtime could be better controlled. From the aspect of long-term treatment, the decreased whole-day glucose variance after treatment with glargine might better improve DM patients' prognosis and delay complication than NPH.

Therefore, CGMS can give detailed description of whole-day glucose variance of DM patients receiving oral hypoglycemic agents and (or) insulin therapy, objectively display all time-point glucose profiles and effectively measure the incidence of nocturnal hypoglycemia. According to CGMS examination, compared with traditional basal insulin replacement, once daily subcutaneous injection of glargine is superior to NPH in stabilizing whole-day glucose level and reducing the incidence of nocturnal hypoglycemia, so it is a more ideal basal insulin replacement.

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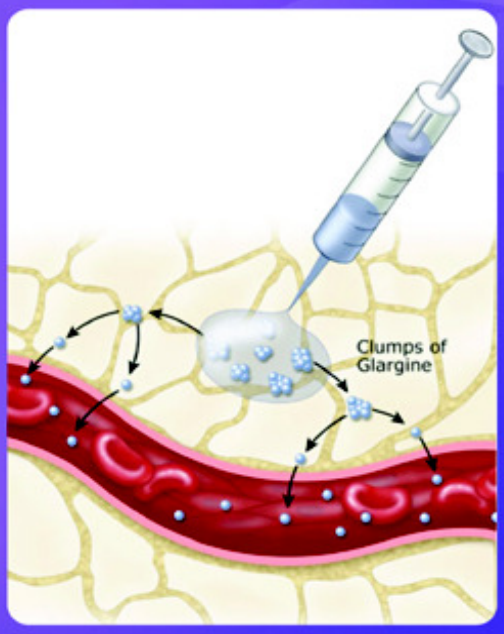
Glargine – How it absorbs?

- ✓ After subcutaneous injection, glargine form micro precipitates
- ✓ Sustained, slow release over 24 hours
- ✓ Peakless insulin
- ✓ Closely mimics the physiological insulin secretion



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