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Original Article

Effect of combined application insulin and insulin detemir on continous glucose monitor in children with type 1 diabetes mellitus

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Abstract: Insulin detemir is a soluble long-acting human insulin analogue at neutral pH with a unique mechanism of action, which could strengthen the effects of insulin. This study aims to explore the effects of insulin combined with insulin detemir on the continous glucose in children with type 1 diabetes mellitus. In this study, 150 patients with type 1 diabetes enrolled were included and randomly divided into 3 groups: insulin group (group A), insulin detemir group (group B) and insulin combined with insulin detemir group (group C). Each subject underwent 72 h of continuous glucose monitoring (CGM). MAGE, HbA_{1c} and Noctumal Hypoglycemia levels were examined by using the ELISA kits. The body weight changes were also detected in this study. The results indicated that the information including age, body weight, disease duration and glucose level and HbA_{1c} percentage on the start time point among three groups indicated no statistical differences. Insulin combined with insulin detemir decrease MAGE and HbA_{1c} level in Group C compared to Group A and Group A ($P < 0.05$). Insulin combined with insulin detemir decreas noctumal hypoglycemia levels and body weight changes ($P < 0.05$). In conclusion, this study confirmed efficacy of insulin detemir by demonstrating non-inferiority of insulin detemir compared with insulin with respect to HbA_{1c}, with an improved safety profile including significantly fewer hypoglycaemic episodes and less undesirable weight gain in children.

Keywords: Diabetes mellitus, insulin detemir, hypoglycemia, insulin therapy

Introduction

Insulin was discovered 80 years ago [1], and has been applied to clinical treatment medication for many years. Insulin detemir is a soluble long-acting human insulin analogue at neutral pH with a unique mechanism of action [2]. Following subcutaneous injection, insulin detemir binds to albumin via fatty acid chain, thereby providing slow absorption and a prolonged metabolic effect [3]. Insulin detemir has a less variable pharmacokinetic profile than insulin suspension isophane or insulin ultralente [4]. The use of insulin detemir can reduce the risk of hypoglycemia (especially nocturnal hypoglycemia) in type 1 and type 2 diabetic patients [5]. However, overall glycemic control, as assessed by glycated hemoglobin, is only marginally and not significantly improved compared with usual insulin therapy. The weight gain commonly associated with insulin therapy is rather limited when insulin detemir is used [6]. In our experience, this new insulin analogue is preferably administrated at bedtime but can be proposed twice a day (in the morning and either before the dinner or at bedtime). Thus insulin detemir is a promising option for basal insulin therapy in type 1 diabetic patients.

Material and methods

Patients

150 patients with type 1 diabetes enrolled in our hospital were randomly divided into 3 groups: insulin group (group A), insulin detemir group (group B) and insulin combined with insulin detemir group (group C). Patients were prescribed insulin and/or insulin detemir at their physician's discretion for 3 months. The drug

Table 1. Clinical characteristic description at onset time point of experiment

Parameters	Group A	Group B	Group C	*P* value
n	47	48	48	_
Age (years)	14.5±5.1	15.2±5.7	14.2±6.1	> 0.05
Body weight (kg)	55±9.2	64±10.7	58±9.4	> 0.05
Disease duration (years)	7.4±2.8	7.1±2.7	6.9±3.6	> 0.05
Pre-dinner plasma Glucose (mmol/l)	7.9±3.4	7.1±3.6	7.2±3.8	> 0.05
HbA_{1c} (%)	7.9±0.6	8.1±0.8	7.9±0.9	> 0.05

The demographics, pre-dinner plasma glucose and the percentage of HbA_{1c} were measured and recorded. All quantitative data were represented by mean value ± standard deviations.

dose would be change according the glucose level. Each subject underwent 72 h of continuous glucose monitoring (CGM) using CGMS iPro (Medtronics, Minneapolis, MN) on the last 72 h of each group. For the weight changes examination, we given the patient with the same amounts of dietary, keep the same lifestyle and same amount of exercise.

Excluded criteria: Patients with severe renal insufficiency, diabetic ketoacidosis and patients who received received steroid for any reason. Included criteria: 1) Prepubertal and pubertal age; 2) Absence of acute or chonic inflammatory and autoimmune diseases; 3) No current regular medications.

Primary and secondary endpoints

The primary endpoint was the frequency of serious adverse drug reactions, including major hypoglycaemia. Secondary endpoints included minor and nocturnal hypoglycaemia, glycaemic control (HbA_{1c}, fasting blood glucose and variability of fasting blood glucose) and weight change.

Statistical analysis

Statistical analyses were performed using SPSS software. Nonparametric (Kruskal-Wallis) or X^2 statistics were used for comparison among groups followed by the Holm adjustment for multiple comparisons. *P* values < 0.05 were considered statistically significant.

Results

Demographics

150 pediatric subjects with type 1 diabetes were recruited for this 3 months, randomized and open-labeled study. Patients with serious hypoglycemia discontinue trial for sport or CGM machine reason was excluded from the final statistical analysis. The final subjects in each group were shown in **Table 1**. These patients' general information including age, body weight, disease duration and glucose level and HbA_{1c} percentage on the start time point were without any statistical difference (P > 0.05).

Insulin combined with insulin detemir decrease MAGE and HbA_{1c} level

To confirm the clinical efficiency, CGM was used to monitor the glucose dynamic change in three groups. According to the original data collected by CGM, MAGE (Mean Amplitude of Glycemic Excursions) was calculated by software and used as the main indicator for treatment effect, which were (7.2±3.4) mmol/L in insulin only group, (6.9±4.3) mmol/L in detemir only group and (5.4±2.8) mmol/L in insulin combined with insulin detemir group (**Figure 1A**, P < 0.05).

HbA_{1c} level was used as long-term treatment effect indicator [7]. For 3 groups, the HbA_{1c} level was (7.9±0.8) percent, (7.8±0.6) percent and (7.2±0.3) percent respectively. There was significant statistical difference within 3 groups (P < 0.05). But when compared group A with group B, no significant difference was found in both MAGE level and HbA_{1c} level (**Table 2**; **Figure 2B**, P < 0.05).

Insulin combined with insulin detemir decreas nocturnal hypoglycemia levels and body weight changes

150 subjects were enrolled in the trail while completed this three-months, randomized, open-labeled study. Seven subjects dropped out because of severe hypoglycemia, very active sports schedule and/or could not continue participation. The incidence of serious adverse drug reactions was 30 in total in this study (**Figure 2**). In all three cohorts, the overall minor and nocturnal hypoglycemic events were

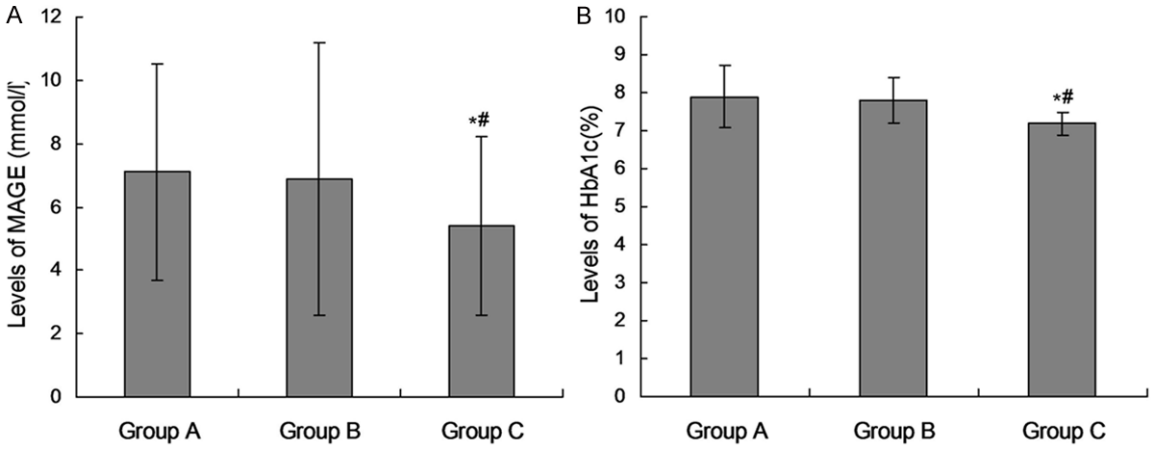

Figure 1. MAGE and HbA_{1c} levels in the three groups. A. Levels of MAGE in every groups. B. Levels of HbA_{1c} in every groups. *P < 0.05 and #P < 0.05 represent the MAGE or HbA_{1c} in Group C compared to Group A and Group B, respectively.

Table 2. MAGE and HbA_{1c} of each group based on CGM

Parameters	Group A	Group B	Group C	*P* value
MAGE (mmol/l)	7.1±3.4	6.9±4.3	5.4±2.8	< 0.05
HbA_{1c} (%)	7.9±0.8	7.8±0.6	7.2±0.3	< 0.05

Glucose dynamic changes in three groups were monitored by CGM and computed. MAGE then calculated based on the results and represented by mean value ± standard deviations. HbA_{1c} level was measured and used as long-term treatmenteffect indicator which were represented by mean value ± standard deviations. *indicates that P < 0.05.

reduced from baseline (P < 0.05). However, in group C both the nocturnal hypoglycemia and body weight change were with statistical difference from the other 2 groups (**Figure 2A**, **2B**, P < 0.05). The nocturnal hypoglycemia occurrence was dramatically lower in group C than in group A and B.

Discussion

The challenge of achieving well-controlled glycemic level is more difficult in pediatric patients compared with adults because of many factors [8], such as social status, diabetes care in school or day care, sports, highly variable lifestyle.

This trial was designed to compare the clinical efficacy of insulin with/without insulin detemir on glycaemic control in children with type 1 diabetes duration more than 2 years.

Within-subject variation in fasting plasma glucose measurements assessed by self-monitored plasma glucose at 52 weeks was lower with insulin detemir than with NPH in the total cohort (SD 3.01 vs. 3.68 mmol/L, P < 0.001).

The slight increase in HbA_{1c} seen with insulin detemir and NPH reflects the difficulties in treating children for whom many factors, including social status, diabetes care in school or day care, highly variable lifestyle and (fear of) hypoglycaemia, influence glycaemic control.

The prognosis of diabetes mellitus (DM) and chronic complications development in these patients are not only closely related to the overall level of blood glucose, but also tightly relevant to glucose variability [9, 10], which can indicate the prognosis in a certain extent. Hypoglycemia is one of serious acute complications of diabetes. The new development of glucose monitor, continuous glucose monitoring system, can give us fully integrated information about glucose dynamic changes in the whole day, especially about the occurrence of nocturnal hypoglycemia. Researchers reported that higher glucose variability induce more frequent hypoglycemia which increase the incidence of cardiovascular events [11, 12]. Thus, it is important to take effective measures to lower patients' glucose variability. In this trail, patients with insulin and detemir combined treatment reach a decreased glucose variability and lower hypoglycemia frequency compared with patients with insulin or determir only treatment. Patients treated with insulin detemir in a clinical healthcare setting improved their glycemic

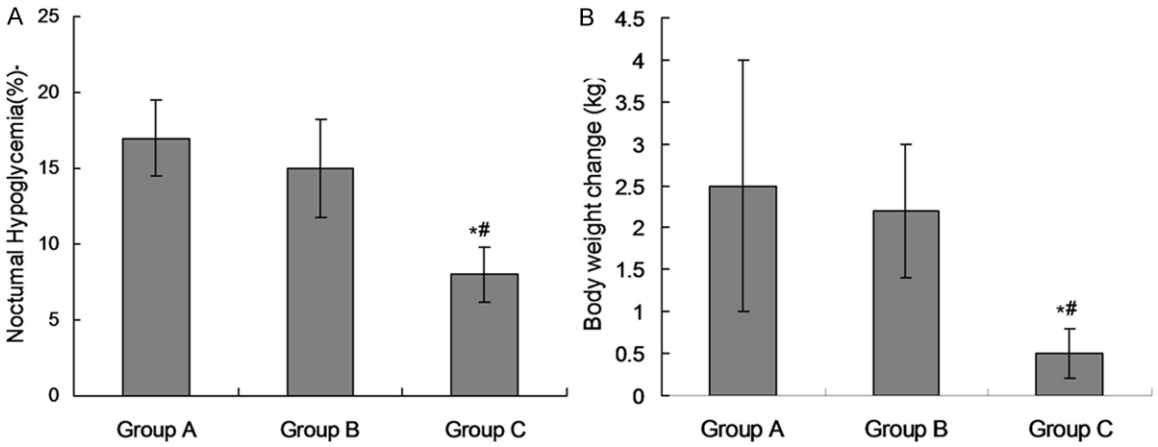

Figure 2. Noctumal Hypoglycemia levels and Body weight changes in the three groups. A. Levels of Noctumal Hypoglycemia in every groups. B. Body weight changes in every groups. $^{*}P < 0.05$ and $^{\#}P < 0.05$ represent Noctumal Hypoglycemia levels and Body weight changes in Group C compared to Group A and Group B, respectively.

control with no increases in hypoglycemia, adverse events or weight compared with baseline.

In conclusion, this study confirmed efficacy of insulin detemir by demonstrating non-inferiority of insulin detemir compared with insulin with respect to HbA_{1c}, with an improved safety profile including significantly fewer hypoglycaemic episodes and less undesirable weight gain in children.

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Disclosure of conflict of interest

None.

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