Analysis of alternatives for insulinizing patients to achieve glycemic control and avoid accompanying risks of hypoglycemia

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Abstract. The aims of the present study were to explore the efficacy of glycemic control and the risks of hypoglycemia with different methods of insulin therapy, and to provide reference data for the clinical treatment of diabetes. In this retrospective study, hospitalized patients diagnosed with type 2 diabetes between March and December 2014, in the Department of Endocrinology in the First Affiliated Hospital of Wannan Medical College, were divided into three groups, including an intensive insulin analogue therapy group, a premixed insulin analogue treatment group and a premixed human insulin therapy group. The efficacy of glycemic control and the incidence of hypoglycemia were determined in each of the insulin treatment groups. Compared with the other treatment groups, the intensive insulin analogue therapy group was associated with superior blood glucose control, shorter time to reach standard insulin regimen, shorter hospitalization time, fewer fluctuations in blood glucose levels and lower insulin dosage on discharge from hospital. However, this treatment was also associated with a high risk of hypoglycemia. In conclusion, when combined with the effective prevention of hypoglycemia and appropriate nursing care (especially in hospital care), intensive insulin analogue therapy may provide the greatest benefit to patients.

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Introduction

Diabetes is a group of metabolic endocrine diseases that are characterized by hyperglycemia. Due to its high incidence and multiple complications, diabetes is the third biggest disease threat to human health in disease burden and morbidity, after oncological and cardiovascular diseases (1). The advent of treatment with insulin was a revolution in the treatment of diabetes and has made it possible to more effectively control diabetes and hyperglycemia. The pathogenesis of type 1 and type 2 diabetes involves the absolute or relative lack of islet function. Therefore, in type 1 diabetes and adult-onset type 2 diabetes, the administration of exogenous insulin is the most effective form of treatment. Furthermore, the early use of insulin therapy in type 2 diabetes is hypothesized to be important in slowing the course of this disease (2). Insulin analogues and human insulin, and the corresponding premixed preparations are widely used in clinical practice. Blood glucose fluctuation has been perceived as an independent risk factor that contributes to vascular complications in patients with diabetes, while hypoglycemia is the main risk associated with insulin therapy (3). The present study investigated the effects of different insulin therapies on glycemic control and fluctuations of blood sugar levels, and evaluated the risks of hypoglycemia with these approaches, in order to provide a reference for the selection of insulin therapy in clinical practice.

Subjects and methods

Ethics approval. This study was approved by the ethics committee of Yijishan Hospital of Wannan Medical College (Wuhu, China). Patient consent was also obtained. Witten informed consent was obtained from the patient.

Relevant standard. When making the diagnosis of diabetes, the 'WHO 1999 diabetes diagnostic criteria' were referred to (4). Criteria for inclusion in the study were: i) age 35-75 years and body mass index (BMI) ≤30 kg/m^2; and ii) no severe renal impairment, serum creatinine ≤133 μmol/l, and no hypoglycemia, infection, ketoacidosis or acute complications, such as water and electrolyte disorders or acid-base imbalances. Exclusion criteria were: i) type 1 diabetes; ii) pregnancy; and

iii) treatment with the oral hypoglycemic agents, sulfonylureas or non-sulfonylurea secretagogues.

Patient selection and treatment. In this retrospective study, conducted from March to December 2012 at the Wannan Medical College (Wuhu, China), patients requiring hospital treatment for type 2 diabetes, were predominantly newly diagnosed patients with severe type 2 diabetes, in addition to a number of older patients with type 2 diabetes (with prior use of sulfonylureas or non-sulfonylurea secretagogues oral hypoglycemic drugs) who exhibited poor control of blood glucose. A total of 145 patients with type 2 diabetes were selected, according to the inclusion and exclusion criteria, of which 89 were male and 85 were female. A healthy diet and exercise are advised as an important component of diabetic care. Subjects were divided into three groups according to treatment. The first group consisted of those given intensive insulin analogue therapy (55 cases), using insulin aspart, a new fast-acting human insulin analog [IAsp; Novo Nordisk (China) Pharmaceuticals Co., Ltd., Tianjian, China], as a subcutaneous injection prior to meals, in addition to the subcutaneous long-acting insulin, glargine (Lantus®; Sanofi-Aventis Pharmaceuticals), at bedtime. The second group consisted of those given a premixed insulin analogue (48 cases), with a subcutaneous injection of the two-phase insulin, aspart 30 [Novo Nordisk (China) Pharmaceuticals Co.], prior to breakfast and dinner, and before lunch when required. The final groups consisted of those given a premixed human insulin (42 cases), Novolin® 30R [Novo Nordisk (China) Pharmaceuticals Co.]. Depending on blood glucose levels, patients in the three groups took metformin and added acarbose when required. The initial insulin dosage of patients was estimated by an experienced senior doctor, according to the level of blood glucose and the patient's BMI as well as indicators such as present illness, past history, eating habits, age, presence or absence of complications and kidney function. Initially, a total daily dose of 20-26 units of insulin was prescribed. The insulin allocation for the intensive insulin analogue group was as follows: Before breakfast, a quarter of the total dose; before lunch and dinner, a fifth of the total dose; with the residual dose at bedtime in the form of insulin glargine. For the premixed insulin analogue group, the initial allocation scheme was as follows: Before breakfast, three-fifths of the total dose; before dinner, the remaining two-fifths of the total. For the premixed human insulin group, the initial allocation was as follows: Before breakfast, two-thirds of the total dose; before dinner, the remaining dose. Blood glucose levels were measured prior to breakfast in order to adjust the dose of insulin. If the pre-meal blood glucose was <3.9 mmol/l, subjects were advised to eat and to reduce the corresponding pre-dinner insulin dose by 2-4 units. If the pre-meal blood glucose was 3.9-8.0 mmol/l, the insulin dose was not altered. If the pre-meal blood glucose was 8.0-11.1 mmol/l, subjects were advised to increase the corresponding pre-dinner insulin dose by 2 units. If the pre-meal blood glucose was >11.1 mmol/l, subjects were advised to increase the corresponding pre-dinner insulin dose by 2-4 units and adjust the timing for the next insulin dose to after breakfast the following day.

Blood glucose monitoring. During hospitalization, a Johnson & Johnson steady glucose meter [Johnson & Johnson Medical (China) Ltd., Shanghai, China] was used to monitor blood glucose levels prior to and following meals, and before going to bed (10 p.m.); a total of seven times per day. A total of 75 patients, including lower blood sugar in 10 p.m. and with previous history of hypoglycemia, were required to add measurements during the night (00:00 and 03:00). Peripheral capillary whole blood glucose was monitored by fingertip sampling.

Measurement of targets. Each subject's height, weight, age, duration of diabetes and BMI were recorded, together with a fasting blood glucose, glycosylated hemoglobin, serum creatinine, and total cholesterol and triglyceride levels, determined from blood samples collected on the second day of admission. Statistical grouping of all peripheral capillary blood glucose standard deviations reflected the overall blood sugar fluctuations. Statistical grouping of all the variation coefficients of peripheral capillary blood sugar levels taken on an empty stomach gave the coefficient of variation of fasting blood glucose (FBG-CV; the ratio of the standard deviation and mean), reflecting fasting blood glucose fluctuations. On two consecutive days, fasting blood glucose of ≤7 mmol/l and 2-h postprandial blood glucose of ≤10 mmol/l were designated as standard glucose control (5). The ratio of the number of hypoglycaemia and the total number of peripheral blood glucose monitoring gave the hypoglycemia occurrence frequency at each time point of the distribution statistics of hypoglycemia: On an empty stomach, 2 h after breakfast, 2 h after lunch and 2 h after dinner, and at another five points in time (prior to lunch and dinner, 10 p.m., 0 and 3 a.m.). Diagnostic criteria were as follows: For hypoglycemia, blood glucose ≤3.9 mmol/l; for severe hypoglycemia, blood glucose ≤2.8 mmol/l (5). The frequency of hypoglycaemia were defined (calculated) as the ratio of the numbers of hypoglycaemia and the total numbers of peripheral blood glucose monitoring, whereas the frequency of severe hypoglycaemia were calculated as the ratio of the numbers of severe hypoglycaemia and the numbers of hypoglycaemia.

Statistical methods. SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. If the data conformed to a normal distribution (mean ± standard deviation), groups were compared using the Student's t-test. The constituent ratio of data was expressed as a ratio. Groups were compared using the χ^2-square (4x2) test. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of general characteristics. Three groups of patients were included in the present study: An intensive insulin analogue group (group A), with 55 cases; a premixed insulin analogue group (group B), with 48 cases; and a premixed human insulin group (group C), with 42 cases. The general clinical baseline data for the three groups are shown in Table I. From the general data pairwise comparison, no statistically significant differences were observed between the three sets of baseline data.

Glycemic control. A total of 145 patients monitored their blood sugar levels throughout the day during hospitalization, and a total of 62 patients maintained blood glucose control at the target levels. Among these patients, 28 cases were from the

Table I. General clinical data for each group.

Group (no. of cases)	Age, years	BMI, (kg/m^2)	Course of disease, (years)	BG, (mmol/l)	CHOL, (mmol/l)	TG, (mmol/l)	LDL, (mmol/l)	SCr, (mmol/l)	HbA1c, (%)
A (55)	56.7±8.2	22.1±2.8	4.7±1.5	10.9±4.5	4.7±1.35	1.7±0.3	3.36±0.45	75.3±17.6	10.2±1.9
B (48)	53.6±7.3	22.7±2.6	5.5±1.7	9.8±4.2	4.55±1.21	1.8±0.37	3.22±0.38	77.6±19.2	9.7±1.85
C (42)	52.5±6.5	21.9±2.5	4.8±1.6	9.6±3.9	4.32±1.19	1.65±0.32	3.33±0.29	72.5±21.1	9.5±1.75

Group A, intensive insulin analogue group; group B, premixed insulin analogue group; group C, premixed insulin group. No significant differences were detected between the three groups for any of the factors. P>0.05 for all comparisons. BMI, body mass index; BG, blood glucose; CHOL, cholesterol; TG, triglyceride; LDL, low-density lipoprotein; SCr, serum creatinine; HbA1c, glycosylated hemoglobin.

Table II. Comparison of glycemic control between the three groups.

Group	Total patients	Standard glucose control patients	Standard glucose control rate, (%)	Time to reach standard (days)	Number of cases requiring acarbose	Acarbose use (percentage)
Intensive insulin analogue	55	28	50.9[a]	3.5±1.2[a]	5	9.09[a]
Premixed insulin analogue	48	18	37.5	6.2±1.5	38	79.16
Premixed human insulin	42	16	38.1	6.7±1.3	35	83.33

[a]P<0.01, compared with the premixed insulin analogue and premixed human insulin groups.

standard intensive insulin analogue group, in which the standard rate of glycemic control was 50.9%; 18 cases were from the standard premixed insulin analogue group, in which the standard rate of glycemic control was 37.5%; and 16 cases were from the standard premixed insulin group, in which the standard rate of control was 38.1%. The intensive insulin analogue group achieved a rate that was significantly higher than that of the other two groups (P<0.01). In addition the time taken to achieve standard glucose control was also significantly shorter in the intensive insulin analogue group compared with the other groups (3.5±1.2 days; P<0.01). Furthermore, the intensive insulin analogue group required less acarbose in order to achieve postprandial blood glucose control; in this group, the acarbose utilization rate was only 9.09%. By contrast, the acarbose utilization rates for the premixed insulin analogue group and the premixed human insulin group were 79.16 and 83.33%, respectively. These differences were significant (P<0.01), as shown in Table II.

Insulin dosage at hospital discharge and duration of hospitalization. In the intensive insulin analogue group, insulin dosage was 29.2±9.7 units at discharge, and hospitalization was 8.8±1.7 days. For the premixed insulin analogue group, the discharge dosage was 35.5±12.3 units and hospitalization was 10.6±2.1 days. In the premixed human insulin group, the discharge dosage was 37.6±13.7 units and hospitalization was 11.3±2.4 days. At discharge the dosage of insulin was lowest for the intensive insulin analogue group, with a statistically significant difference (P<0.05). In addition, this group had

Table III. Insulin dosage at discharge length of hospitalization.

Group	Cases	Discharge insulin, (U/d)	Hospitalization (days)
Intensive insulin analogue	55	29.2±9.7[a]	8.8±1.7[a]
Premixed insulin analogue	48	35.5±12.3	10.6±2.1
Premixed human insulin	42	37.6±13.7	11.3±2.4

[a]P<0.05 compared with the premixed insulin analogue group and premixed human insulin group.

the shortest hospital stay, also with a statistically significant difference (P<0.05), as shown in Table III.

Comparison of the prevalence of hypoglycemia. Among the three groups of patients, a total of 5,651 peripheral blood sugar monitoring data points were collected, including 1,983 for the intensive insulin analogue group, 1,886 for the premixed insulin analogue group and 1,782 for the premixed human insulin group. Of a total of 210 episodes of hypoglycemia, the number of episodes of severe hypoglycemia was 64. The frequency of hypoglycemia for the intensive insulin analogue group was higher than the other groups, at 44.9% (P<0.05), and the intensive insulin analogue group also experienced the

Table IV. Comparison of hypoglycemia between the treatment groups.

Group	Cases	Number of peripheral blood glucose readings	Number of hypoglycemic episodes	Frequency of hypoglycemia (%)	Number of severe hypoglycemic episodes	Frequency of severe hypoglycemia (%)	Proportion of patients with severe hypoglycemia (%)
Intensive insulin analogue	55	1,983	89	4.49[a]	32	16.1[a]	35.9[a]
Premixed insulin analogue	48	1,886	62	3.29	17	9.0	27.4
Premixed human insulin	42	1,782	59	3.31	15	8.4	25.4

[a]$P<0.05$, compared with the premixed insulin analogue and premixed human insulin groups.

Table V. Comparison of blood glucose fluctuation with each form of insulin therapy.

Group	Cases	Number of peripheral blood glucose readings	Blood sugar level standard deviation, (mmol/l)	Fasting capillary blood glucose	Number of fasting blood glucose variation coefficient (%)
Intensive insulin analogs	55	1,983	3.95[a]	291	37.1[b]
Premixed insulin analogue	48	1,886	5.76	273	43.7
Premixed human insulin	42	1,782	5.82	265	44.6

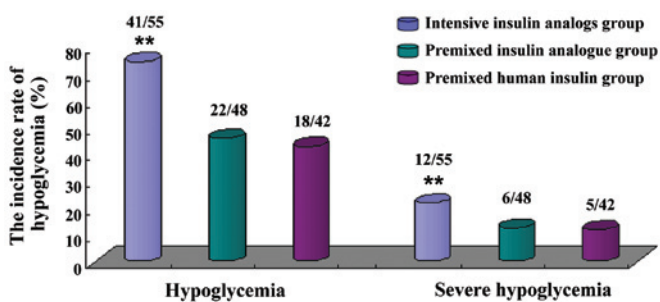[a]$P<0.01$ and [b]$P<0.05$, compared with the premixed insulin analogue and premixed human insulin groups.

Figure 1. Percentage of patients experiencing hypoglycemia and severe hypoglycemia in the three insulin therapy groups. **$P<0.01$, compared with premixed insulin analogue and premixed human insulin group groups.

highest occurrence of severe hypoglycemia (16.1%; $P<0.05$), as shown in Table IV. The proportion of patients who had at least one episode of hypoglycemia in individuals within the three groups was also examined. In the intensive insulin analogue group (55 cases), there were 41 cases of hypoglycemia, including 12 cases of severe hypoglycemia. Thus the incidence of hypoglycemia and severe hypoglycemia was 74.5 and 21.8%, respectively. In the premixed insulin analogue group the incidence was 45.8 and 12.5%, respectively. In the premixed human insulin group the incidence was 42.8 and

11.9%, respectively. Therefore, the intensive insulin analogue group exhibited the highest incidence of hypoglycemia and severe hypoglycemia ($P<0.05$). No significant differences were detected between the other two groups, as shown in Fig. 1.

Blood glucose fluctuations associated with different insulin therapies. The blood glucose level standard deviation is a good representation of blood glucose fluctuations. For the three groups of patients, statistical analysis revealed a standard deviations of 3.95 mmol/l for the intensive insulin analogue group, 5.76 mmol/l for the premixed insulin analogue group and 5.82 mmol/l for the premixed human insulin group. Since the fasting blood glucose is relatively stable, FBG-CV can reflect the blood glucose fluctuations. FBG-CV was 37.1% for the intensive insulin analogue group, 43.7% for the premixed insulin analogue group and 44.6% for the premixed human insulin group. Therefore, the intensive insulin analogue group had the lowest variation coefficient, compared with the other two groups ($P<0.01$; Table V).

Discussion

Strict glycemic control is an important measure by which to prevent and reduce the numerous complications of diabetes. Insulin has a vital role in the treatment of diabetes. In addition,

the functioning of pancreatic β cells is affected, to different degrees, in the majority of patients with type 2 diabetes. There are varying degrees of defects in the phases of insulin secretion. In the first phase, a defect in secretion is the primary cause of postprandial hyperglycemia. Therefore, the appropriate use of insulin may simulate the reconstruction of the physiological insulin secretion phase, promptly control blood sugar levels and reduce toxicity resulting from high sugar levels, which causes damage to the islet cells, thereby restoring the function of islet β cells (6,7). However, excessively strict glucose control also increases the risk of cardiovascular events in diabetic patients, which is clearly counter-productive (8). Therefore, determining how to safely and effectively utilize insulin, and familiarity with the advantages and disadvantages of various insulin therapies, helps to provide clinical staff with appropriate guidelines for the diagnosis, treatment and nursing care of patients with diabetes.

The present study selected three widely-used types of insulin in order to control blood sugar levels: An intensive insulin analogue, a premixed insulin analogue and a premixed human insulin. Among these options, the intensive insulin analogue included insulin aspart, with a proline amino acid at human insulin B28 replaced by aspartic acid. Due to the substitution of the B28 proline residue for aspartate, the tendency of human soluble insulin to form hexamers is greatly reduced in insulin aspart. Therefore, insulin aspart has a number of advantages, including a faster subcutaneous absorption rate and and can be given closer to meal times. Its duration of action is shorter and it is therefore effective at reducing postprandial blood glucose, although it often requires combination with a long- or intermediate-acting insulin, in order to achieve good control of fasting blood glucose. However, as a result of the higher frequency of administration, the compliance of patients was generally poorer with this preparation. The premixed insulin analogue group received insulin aspart 30 injections, which contained biphasic insulin aspart, composed of 30% soluble insulin aspart and 70% protamine insulin aspart (a short-acting agent). This is usually administered twice per day (prior to breakfast and dinner). It may also be taken three times a day (before each meal) in order to achieve better control of blood glucose. As fewer injection were required in this group relative to the intensive treatment group, long-term compliance was generally better. The premixed human insulin treatment group received protamine zinc recombinant human insulin (Novolin 30R). It contained 30% soluble human insulin and 70% isophane insulin. The speed of onset is half an hour; thus the dose is given 15-30 min prior to meals.

Analysis of glycemic control and the risk of hypoglycemia in the different groups was performed. The results showed that the intensive insulin analogue treatment groups was superior in terms of glycemic control as well as the time taken to achieve the blood glucose target. That is, the standard rate of glycemic control was higher, the time taken to achieve control was shorter and blood glucose fluctuations were smaller. These factors may all help to reduce the length of hospital admissions. Compared with the other treatment groups, patients in the intensive insulin analogue group required a significantly lower dose of insulin at discharge. This suggests that a good recovery of islet function had occurred following short-term intensive insulin treatment. Furthermore, the intensive insulin analogue group exhibited better control of postprandial glucose levels, with a significantly

lower percentage of patients in this group requiring treatment with acarbose drugs, compared with patients in the premixed insulin aspart 30R and premixed human insulin groups. The mainly reason for this phenomena may be the different diet habits between China and the west. the larger proportion of carbohydrate were intook in Chinese whereas insulin aspart 30R and human insulin Novolin® 30R only include 30% available or short acting components, which could be more effective on postprandial blood glucose. However, the Chinese diet is characterized by carbohydrates that given priority to. Therefore, it is challenging to effectively control the postprandial blood glucose peak, and the use of α-glycosidase inhibitors is frequently required. However, although good blood glucose control and improved islet function were achieved using the intensive insulin analogue treatment, more hypoglycemic events and a significantly higher frequency of hypoglycemia were recorded in this group. In particular, the proportion of severe hypoglycemic events increased significantly. Severe hypoglycemia may induce detrimental cardiovascular events (8,9), and is thus a significant adverse reaction of this method of treatment. Therefore, intensive insulin treatment should be combined with an awareness of the risk of hypoglycemia, and the use of preventive and active measures in order to reduce the likelihood of patients experiencing this problem. Using this approach, intensive insulin analogue treatment may provide the greatest benefit to patients.

Acknowledgements

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