

COMBINATION INSULIN THERAPY WITH PRE-MIXED INTERMEDIATE/RAPID-ACTING INSULIN (70/30) AND INSULIN LISPRO MIMICKING PHYSIOLOGIC INSULIN SECRETION: OPTIMAL GLYCEMIC TREATMENT WITH SUSTAINABILITY OF CONTROL IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Background: Physiologic pancreatic response to glucose load yields two peaks of insulin secretion: the first peak within 30 minutes, and the second on the 2nd to 3rd hour after the stimulus.

Objective: Our aim was to show that a combination therapy designed to mimic this insulin secretion obtains optimal glycemic control with sustainability.

Methods: In this descriptive retrospective study, we measured glycemic control and sustainability in terms of reduction in HbA1c and postprandial capillary blood glucose (pCBG) between patients on insulin 70/30 with lispro and insulin 70/30 alone. We reviewed records of 218 patients (153 females; 65 males) in an outpatient endocrinology clinic. Initial and follow-up pCBG (2 to 4 hours after lunch) and HbA1c were measured and compared among study groups. Metformin 1000 to 1500 mg daily was given in combination with insulin.

Results: There was a significant reduction (33%) in pCBG from baseline in patients (n=141) placed on premixed insulin alone (p value <0.0005). A greater significant reduction (45%) in pCBG was obtained in patients (n=39) on premixed insulin and lispro (p value <0.009). Serial HbA1c determination (n=78) showed an initial reduction of 17.5% (from 9.07% to 7.48%) within a mean duration of 7 months (3-21 months). On further follow-up with a mean duration of 5.7 months (3-15 months), a sustained reduction of 18% in HbA1c (mean at 7.44%; n=23) was noted. With automatic snacking instructions, hypoglycemic episodes were insignificant.

Conclusion: Combination insulin therapy with 70/30 and lispro mimicking physiologic insulin secretion

yielded sustainability of glycemic control (18% HbA1c reduction) in type 2 DM patients.

Keywords: combination insulin, insulin 70/30, lispro

INTRODUCTION

The U.K. Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control reduced the overall risk of diabetic eye disease, kidney damage, stroke, and overall mortality.¹ Whereas diet and exercise have been demonstrated to delay the onset of type 2 diabetes by improving glycemic control early in the course of the disease, the success rate of such conventional management regimens in the long term is poor.

Oral hypoglycemic agents often become the mainstay of type 2 diabetes treatment.² After three years of monotherapy, however, nearly 50% of subjects were unable to maintain their target levels of glycosylated hemoglobin and will require more than one pharmacologic agent.^{3,5} Most patients with type 2 diabetes will eventually need insulin. UKPDS likewise showed that [beta]-cell failure is progressive; only 50% of normal [beta]-cell function at diagnosis with a steady decline following diagnosis.⁴ Using UKPDS data, Turner *et al.* found that when the subjects were treated with diet, insulin, or sulfonylureas, only 8%, 42%, and 24%, respectively, were able to maintain glycosylated hemoglobin levels below 7% after 9 years.⁵

A significant reduction (25%) in microvascular complications was achieved with intensive therapy that lowered HbA1c levels to a median of 7% over 10 years when compared to conventional treatment that achieved a median HbA1c of 7.9%. For every percentage point decrease in HbA1c, there was a 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and 18% reduction in combined fatal and non-fatal myocardial infarction.⁵

In vivo studies of beta-cell secretory function have demonstrated that insulin is released in a pulsatile manner, with rapid oscillations occurring every

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8-15 minutes superimposed on slower (ultradian) oscillations occurring at a periodicity of 80-150 minutes.⁸ When glucose is infused intravenously at a constant rate, an initial biphasic secretory response is observed that consists of a rapid first phase (Phase I) release of pre-formed insulin occurs, which peaks in 3-5 minutes, followed by a second phase (Phase II) release of newly formed insulin, which begins at 2 minutes and continues to increase slowly for at least 60 minutes or until the stimulus stops.⁷ The beta cell defect in type 2 DM is characterized by an absent Phase I insulin and C-peptide response and a reduced Phase II.⁸

In order to achieve better glycemic control, several combinations of insulin have been marketed and used. Since injected insulin immediately enters the systemic circulation, and endogenous insulin is secreted in the portal venous system, exogenous insulin administration exposes the liver to subphysiologic insulin levels. Also, there is considerable patient-to-patient variation in insulin secretory pattern of the pancreatic islet. Most physiologic regimens require more frequent insulin injections, greater reliance on short-acting insulin, and more frequent capillary plasma glucose measurements. One such insulin regimen consists of a combination of lispro insulin, which acts within 15 minutes and peaks at 1 hour, plus premixed NPH-regular insulin, which acts within 30 minutes and peaks within 2-12 hours. With the peak of action of NPH-regular insulin coinciding with the Phase II release of insulin for basal requirement, and the peak of action of lispro insulin coinciding with the Phase I postprandial rapid release of insulin, this combination regimen mimics the physiologic post-prandial response of insulin to hyperglycemia, as described earlier.

This study is a descriptive retrospective analysis of the combination regimen of premixed insulin and lispro in terms of glycemic control and sustainability thru capillary blood glucose determination and serial HbA1c level measurements.

MATERIALS AND METHODS

We reviewed records of 218 patients (153 females; 65 males) seen in an outpatient specialty endocrinology clinic. Initial and follow-up postprandial capillary blood glucose (CBG) were measured 2 to 4 hours after lunch and compared among study groups. HbA1c levels were also recorded before and during therapy with either premixed insulin alone or with combination premixed insulin and lispro. Both groups were studied and compared in terms of glycemic

control described as a reduction in postprandial CBG and HbA1c. Sustainability of control thru serial HbA1c measurements was studied in the set of patients on combination regimen. Patients who are on steroids, pregnant patients, and DM Type 1 patients were excluded. All patients underwent DM education and automatic snacking instruction (diet composed of 3 main meals per day followed by snacks taken automatically 2 hours postprandial or post-injection of insulin). Metformin 1000 to 1500 mg daily was given in combination with insulin.

Data Analysis

The mean and standard deviation were used to describe the reduction of CBG and HbA1c between study groups at baseline and on follow-up. Data was encoded using a data entry program, and presented graphically. Data processing analysis utilized EXCEL and STATA soft wares to determine significant percentage reduction in glycemic goals.

RESULTS

The study population consists of 218 patients either newly or previously diagnosed with DM Type 2. The clinical characteristics are shown in Table I. Mean age at consult was 57.2 years. Mean duration of diabetes prior to seeking consultation was 7.4 years. Sixty two percent (135/218) of patients was placed on insulin at initial visit (group 1) and 38% (group 2) was maintained initially on oral hypoglycemic agents (OHA) and were shifted to insulin after a mean duration of 1 year. Fifty-five percent in group 1 was placed on insulin at first consult because of DM complications and co-morbidities as follows: macrovascular – arterial occlusive disease, coronary artery disease, and stroke; and microvascular – retinopathy and nephropathy. The 45% in group 1 was placed on insulin despite the absence of complications/ co-morbidities because of any of the combination of the following: a) on maximum dose of tablets, b) HbA1c levels $\geq 8\%$, c) duration of DM was > 7 yrs. There was a significant reduction (33%) in postprandial CBG (pCBG) from baseline in patients (n=141) placed on premixed insulin alone (baseline: 264.2mg/dL; follow-up: 176.8mg/dL, p value < 0.0005). Mean pre-breakfast dose was 26.2 units and mean pre-supper dose was 11.1 units. A greater significant reduction (45%) in pCBG was obtained in patients (n=39) on premixed insulin and insulin lispro (baseline: 301.5mg/dL; follow-up: 166.6mg/dL; p value < 0.009). Mean premixed insulin dose were as follows: pre-breakfast; 23.4 units,

pre-supper; 11.2 units. Mean lispro doses were as follows: pre-breakfast; 7.1 units, pre-lunch; 9.5 units, and pre-supper; 6.4 units. An equally significant reduction in pCBG (42%; p value: <0.001) was seen in patients ($n=38$) started on premixed insulin for a mean duration of 6 months and later given lispro (Figures 1 & 2). Mean reduction in pCBG were 42.3 mg/dL (premixed alone) and 93.6 mg/dL (with added lispro).

Serial glycosylated hemoglobin level determination ($n=78$) showed an initial HbA1c reduction of 17.53% (from 9.07% to 7.48%) within a mean duration of 7 months (3-21 months). On further follow-up with a mean duration of 5.7 months (3-15 months), a sustained improvement in HbA1c (mean at 7.44%; $n=23$) was noted, showing an overwhelming 18% HbA1c reduction from baseline. Overall, the biochemical and clinical improvement was observed starting at 4 weeks after initiation of combination insulin therapy. With automatic snacking, there was insignificant occurrence of hypoglycemic episodes.

Table I. Baseline Characteristics of Study Groups

	Humulin 70/30 (Group A)	Humulin 70/30 + Humalog (Group B)
Age (Years)	54.2 + 10.9	55.8 + 13.8
BMI (kg/m ²)	23.3 + 3.4	24.7 + 4.2
Insulin dose (units)		Humulin 70/30 Humalog
	26.2	23.4 7.1
• Pre-breakfast		
• Pre-lunch		9.5
• Pre-dinner	11.1	11.2 6.4
Random post-prandial clinic CBG (mg/dL)	264.2	301.5

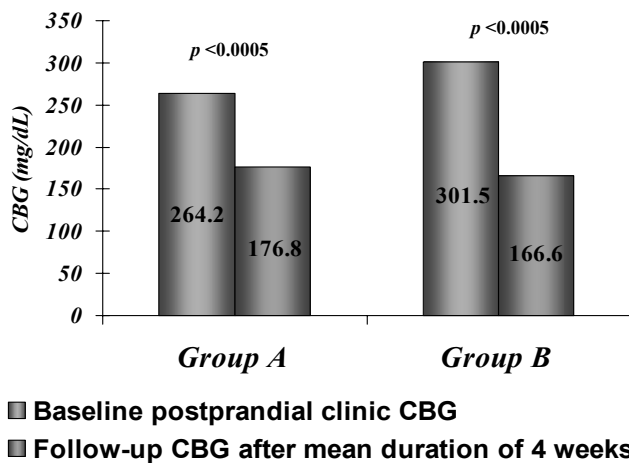


Figure 1. Random CBGs at Baseline and After A Mean Duration of 4 Weeks Follow-up.

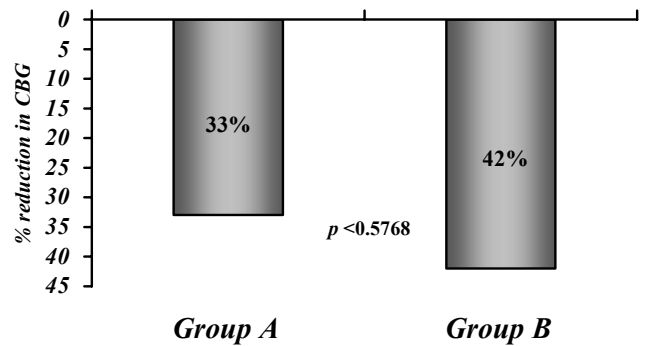


Figure 2. Percentage Reduction in Postprandial CBGs Between the Study Groups.

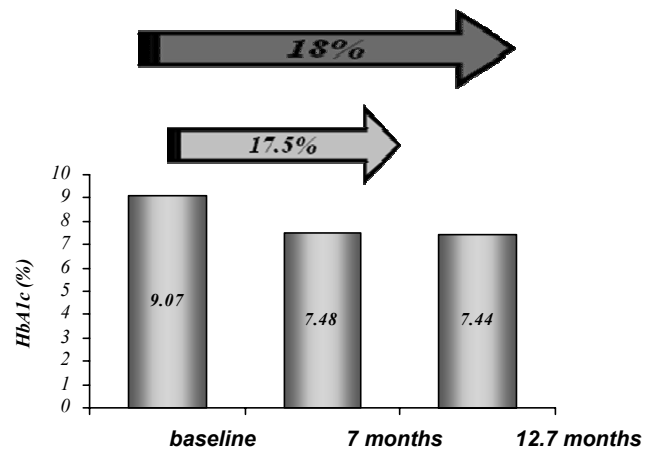


Figure 3. Percentage Reduction in HbA1c of Patients on Premixed 70/30 + Lispro Insulin.

DISCUSSION

The American Diabetes Association (ADA) recommends optimal treatment goals for postprandial glucose levels at 180mg/dL. Accordingly, there are subgroups of type 2 diabetic patients who have average fasting glucose levels within targets but with elevated HbA1c, and that monitoring and specifically treating postprandial elevations in these patients may provide improvements in HbA1c, perhaps with a lower risk of hypoglycemia and weight gain than further lowering fasting and pre-meal glucose levels. The American College of Endocrinology (ACE) recommends targeting a 2-hour postprandial glucose less than 140 mg/dL in an effort to achieve euglycemia. Consistent postprandial glucose values less than 140 mg/dL would be associated with average HbA1c levels of approximately 5%.

Our results indicate a significant reduction in postprandial glucose on both regimens of premixed intermediate and rapid-acting insulin alone and combination premixed insulin and lispro, with higher rates of reduction in the latter regimen. Multiple component insulin regimens have the advantage of providing basal and prandial insulin, and several combinations have been utilized to simulate the insulin secretory pattern of the pancreatic islet cell. Our patients were started on a regimen of premixed intermediate- and rapid-acting insulin, given twice a day, alone (group 1) and in combination with insulin lispro (group 2). The rapid acting insulin which has an onset of ½-1 hr, reduces the peak of postprandial glycemia, while the intermediate acting insulin which has an onset of 13-14 hours, controls basal glycemia due to hepatic gluconeogenesis. This combination, given twice a day, provides glycemic control over a period of 24 hours. By adding insulin lispro, a monomeric analogue which has an onset of 15 minutes given thrice a day, this combination regimen showed a higher reduction in postprandial glucose among our type 2 patients. Such regimen mimics the postprandial and basal phases of insulin release, and provides better glycemic control in terms of postprandial CBG when compared with the premixed insulin regimen alone, as the immediate rise in postprandial glucose is suppressed by the lispro added.

Prospective randomized clinical trials showed improved rates of reduction of microvascular complications in patients with type 2 diabetes treated to lower glycemic targets. In the UK Prospective Diabetes Study (UKPDS), there was a reduction in the risk of microvascular complications (retinopathy, nephropathy, and neuropathy) in the intensive group treated with insulin, and/or oral hypoglycemic agents, with the average HbA1c approximately 1% less than the standard treatment group treated with lifestyle modification and symptom prevention pharmacotherapy. The risk of severe hypoglycemia was on the order of 1% to 5% per year in the insulin-treated group and weight gain was modest. Similar reductions in microvascular events were observed in the Kumamoto study, a Japanese trial which showed HbA1c reduction to approximately 7% maintained for 6 years in patients who achieved target glycemic goals. Both trials showed a modest increased risk of hypoglycemia and weight gain, a reduction in microvascular complications, and a non-statistically significant trend towards reduced macrovascular end points. In the UKPDS epidemiologic analysis, there was a 16% reduction in cardiovascular disease rates per 1% reduction in HbA1c without evidence of a threshold or lower limit of benefit all the way into the normal range. The ADA suggests that the goal

of treatment in the management of diabetes should be an HbA1c value less than 7%. The ACE, on the other hand, has recommended an HbA1c goal of less than 6.5%. However, it should be recognized that there are potential adverse events related to pursuit of more aggressive targets hypoglycemia, long-term exposure to poorly studied combinations of medications, expense, life disruption caused by greater attention and effort to achieve lower glycemic targets, and the potential that great efforts expended in achieving extremely stringent glycemic goals will result in less attention to other health risks by patient or provider.

No cohort of patients of substantial size has ever been reported in which an average HbA1c level less than 7% has been achieved over a time frame that exceeds more than a few months. With the combination regimen of premixed intermediate and rapid acting insulin and insulin lispro, our results showed a 1.6% decrease in glycosylated hemoglobin levels (from 9.07 to 7.48) over a mean duration of 7 months, with sustained improvement (7.44 HbA1c) after a mean duration of 5.7 months, or an overwhelming 18% sustained reduction in HbA1c over a period of 12.7 months. This sustained reduction in HbA1c observed among patients on combination insulin over a period of more than a year shows that such regimen is effective in glycemic control and may prognosticate the delay in onset of micro- and macrovascular complications of DM in this set of patients.

In summary, the use of a combination regimen of premixed intermediate and rapid-acting insulin with lispro which simulates both the physiologic basal and postprandial insulin secretion showed a higher significant reduction in postprandial glucose. This effect is reflected in the reduction of HbA1c by 17.5% over a mean period of 7 months, with sustainability of glycemic control by an overwhelming 18% over the next 5.7 months. We suggest further follow-up of these patients and monitoring of glycemic control in terms of sustained postprandial glucose and HbA1c reduction to target level, as well as determination of onset, or delay, in micro- and macrovascular complications.

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