

Comparison of Efficacy and Safety of Basal and Premixed Insulin Regimens among Type II Diabetes Patients Transiting From Oral Agents to Insulin

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ABSTRACT

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Introduction: Achievement and maintenance of tight glycemic control in type II diabetes require insulin when oral hypoglycemic agents fail to achieve target HbA1C. There is a lack of uniform consensus as to which of the regimens should be recommended to initiate insulin treatment in these patients.

Objectives: To compare the efficacy and safety of adding basal insulin to oral agents versus switching to twice-daily premixed insulin in type II diabetic patients insufficiently controlled by oral hypoglycemic agents (OHAs).

Research design and methods: This was a single-centre, retrospective study comparing glargine+OHA with premixed 70/30 regimen in patients with type II diabetes whose glycemic targets were not achieved with the use of oral hypoglycemic agents.

Results: A total of 138 subjects were eligible for this study. At study end, the mean HbA1c value was lower in the premix 70/30 than in glargine+OHA (8.07 ± 0.15 vs. 8.44 ± 0.17 %, $P < 0.0001$). The HbA1c reduction was greater in the premix 70/30 than glargine+OHA (-2.316 ± 0.25 vs. -2.489 ± 0.24 %, respectively; $P < 0.0001$). More premix 70/30 treated subjects reached target HbA1c values than glargine treated subjects (HbA1c ≤ 7.0 %: 31.4% vs. 26.5%). Similarly, FBG decrease was greater with premix 70/30 (mean difference -54.68 ± 17.93 vs. -68.57 ± 9.178 , $P < 0.0001$), and more patients reached target FBG ≤ 110 mg/dl with premix 70/30 than with glargine+OHA (30% vs. 25%). Premix 70/30 patients had fewer confirmed hypoglycemic episodes than glargine+OHA patients (14.3% and 20.6% respectively).

Conclusion: Based on the results, premixed biphasic 70/30 appears to be more effective than insulin glargine+OHA and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type 2 diabetes that is not optimally controlled on OHA.

Keywords: Diabetes, OHA, retrospective, FBG, HbA1c

INTRODUCTION

Type II diabetes mellitus is a progressive disease. Majority of the patients with type II diabetes are initially treated with dietary and lifestyle modifications and oral hypoglycaemic agents (OHAs). Despite the therapeutic regimen, glycemic control deteriorates with time.^{1,2}

In type II diabetes patients, micro- and macrovascular complications has been associated with poor glycemic control.^{3,4,5} Achieving glycemic control, preferably with hemoglobin HbA_{1c} values of less than 7%, can markedly reduce the risk of such complications.⁶

The American Diabetes Association recommends that the objective of normalizing glycemia and glycosylated hemoglobin concentrations for patients with Type II diabetes should be similar to that for Type I diabetes.⁷

Achievement and maintenance of tight glycemic control require titration of the therapy by initiating insulin when oral

hypoglycemic agents fail to achieve the HbA1C levels to the target. However, only a little proportion of patients having type II diabetes actually can achieve treatment goals and the number of patients requiring insulin therapy eventually rise.^{8,9,10} The results of a UK Prospective Diabetes Study (UKPDS) substudy and large observational PRESENT study revealed that initiation or early addition of insulin to oral therapy further improved the glycemic control in type II diabetic patients.^{11,12}

The optimal insulin regimen in type II diabetes varies among physicians depending on the patient characteristics and guidelines released by diabetes federations. The most convenient and simple ways to initiate insulin treatment in patients with type II diabetes are most probably the use of long-acting basal insulin at bedtime or injection of premixed insulin before one or more meals.

While most studies support the notion that both basal and premixed insulin are better regimens, there is a lack of a uniform consensus as to which of the two regimens should be recommended to initiate insulin treatment in patients with type II diabetes.

The objective of this study is to compare the effectiveness of switching from oral hypoglycemic agents (OHA) to twice-

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daily premixed human 70/30 insulin versus adding a once-daily injection of basal insulin glargine to the prior OHAs.

MATERIALS AND METHODS

This was a single-centre, retrospective study conducted at Asir Diabetes Center from June 2012 to June 2013 in accordance with Good Clinical Practice, comparing basal insulin regimen with premixed biphasic regimen in patients with type II diabetes whose glycemic targets were not achieved with the use of oral hypoglycemic agents. The study protocol was reviewed and approved by the Institutional Review Board.

Patients with Type II diabetes mellitus who were inadequately controlled while receiving oral hypoglycemic agents were recruited in the study after satisfying the following criteria: HbA1c >7%. Exclusion criteria for the study were patients with deranged liver function tests, serum creatinine >1.5 mg/dl, pregnancy, any other acute co-morbid illness, drug dependence and if he/she was unable to understand the regimen.

At the baseline visit, patients were randomized to either insulin glargine (Lantus; Aventis Pharma) given once daily in the morning in combination with the previous oral hypoglycemic agents (glargine plus OAD) or to human premixed insulin (30% regular, 70% NPH insulin; Humulin 30/ 70; Eli Lilly) to be administered twice daily (before breakfast and dinner), while other oral hypoglycemic agents were discontinued (70/30).

Data collected from the patient files included demographic characteristics, medical history, physical examination findings, diabetes related laboratory measurements and treatment recommendations in each visit. The patients were followed up in a scheduled manner every three months and the above data were recorded in each visit.

At the start of treatment, all patients were strictly educated about the application of insulin, use of insulin delivery devices (insulin pens), proper measurement and recording of blood glucose, awareness and management of hypoglycemia and nutrition. The patients were encouraged to self-measure their blood glucose levels every single day of the week at 7-point (before and 2 hours after each main meal and at bedtime) or 4-point (before each main meal and at bedtime) profile and were asked to report their measurements weekly the day after it was done to either diabetes nurse or doctor. At each visit, the patients were asked about compliance with insulin applications, meal planning, any hypoglycemia and its management, and all information gathered was recorded. The insulin dose titrations were done by the doctor.

Efficacy and safety measures:

The primary efficacy measure was the change in HbA1c level from baseline to end point. Secondary efficacy measurements

were mean FBG level, proportion of patients with FBG levels \leq 100 mg/dl and proportion of patients with HbA1c \leq 7.0%. Safety measures were the proportion of patients with hypoglycemic events and the frequency of hypoglycemic events.

Statistical analysis:

The statistical analysis was carried out using graphpad prism version 5.01. All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of skewness and Kolmogorov Smirnov tests of normality. For normally distributed data means were compared using student's t-test for two groups. For time related comparison paired t-test or Wilcoxon signed rank test was applied. Statistical significance considered at $p < 0.05$.

Primary and secondary objectives:

The primary objective of this study was to compare the efficacy and safety of adding once-daily basal insulin versus switching to twice-daily premixed insulin in type 2 diabetic patients insufficiently controlled by oral hypoglycemic agents (OHAs).

The secondary objectives were to investigate the differences in fasting and postprandial blood glucose measurements, rate of improvement in HbA1c or blood glucose measurements, initial and mean insulin doses, incidence and rate of hypoglycemia.

RESULTS

A total of 138 patients were eligible for this study. There were 68 patients randomly assigned to OHA plus glargine (Group 1) and 70 patients were assigned to premix 70/30 (Group 2). Baseline demographic and clinical characteristics such as the age of the patients and the duration of diabetes were nearly similar between the treatment groups (Table 1). But the coexisting complications were more in group 1 patients, as shown in table 1.

Glycemic control:

Glycemic parameters are listed in Table 2. Patients in both groups had statistically significant improvement in the overall glycemic control during the study as evidenced by the decrease in HbA1c levels from 10.76 \pm 0.18 per cent at randomization to 8.44 \pm 0.17 per cent in group 1 and from 10.56 \pm 0.19 per cent to 8.07 \pm 0.15 per cent in group 2 after 12 months of treatment. The mean difference in HbA1c at the end of the study from the baseline in group 1 was -2.316 \pm 0.25 per cent ([95% CI -1.8 to -2.8]) and was comparable with HbA1c reduction of -2.489 \pm 0.24 per cent ([95% CI -2.03 to -3]) in group 2.

Table 1: Baseline Characteristics of the treatment group

Parameters	2 OAD + Glargine	Premix 30/70
N	68	77
Gender (M/F)	38/30	44/26
Age (Years)	52.8±1.2	53.4±1.3
Duration of Diabetes (Years)	10.7±0.7	10.3±0.7
Weight	76.71±1.7	78.72±1.7
BMI	29.67±0.62	31.07±0.86
HbA1c	10.76±1.5	10.56±1.55
FBG	209.8±6.1	208.8 ± 7.4
Co-existing ComplicationsHypertension	22 (32.4%)	17 (24.3%)
Dyslipidemia	54 (79.4%)	27 (38.6%)
Neuropathy	17 (25%)	9 (12.9%)
Retinopathy	9 (13.2%)	3 (4.3%)
Diabetic foot	3 (4.4%)	3 (4.3%)
Impotence	6 (8.8%)	2 (2.9%)
DKA	2 (2.9%)	0 (0)
IHD	6 (8.8%)	1 (1.4%)
CVA	1 (1.5%)	4 (5.7%)
Depression	3 (4.4%)	4 (5.7%)

Of the total 138 patients, only 40 patients achieved HbA1c ≤ 7%, 18 patients (26.5%) from the group 1 and 22 patients (31.4%) from group 2 (p=0.37).

The mean fasting plasma glucose decreased from 209.8±6.1 to 155.1±16.9 mg/dl in group 1 patients and from 208.45±7.53 to 139.92±5.65 mg/dl in group 2 patients. Improvement in FBG was significantly better with premixed 70/30 compared with glargine plus OAD. A greater proportion of patients reached an FBG level ≤ 110 mg/dl with premixed 70/30 than with glargine plus OHA (30% vs 25%). The mean difference in FBG at the end of the study from the baseline in group 1 was -54.68 ± 17.93 mg/dl ([95% CI -54.8 to -86.9]) and -68.57 ± 9.178 mg/dl ([95% CI -50.6 to -86.6]) in group 2.

Weight gain:

Mean weight gain in patients treated with glargine plus OAD and 70/30 was 3.597 ± 2.4 and 4.531 ± 2.9kg, respectively. The mean BMI increased from 29.67±0.62 to 31.07±0.61 kg/m² in group 1 patients and from 31.07±0.86 to 32.82±0.82 kg/m² in group 2 patients.

Insulin dose:

There is a huge difference in the mean total doses of insulin between the two treatment groups at the start of the study; Insulin dose increased over the study duration from a mean daily starting dose of 13.91±1.11 to 32.03±1.86IU at endpoint for insulin glargine. The total dose (prebreakfast dose + predinner dose) increased from the mean starting dose of 50.89±2.66 to 62.54±3.22 IU at endpoint.

The mean difference in insulin dose at the end of the study from the baseline in group 1 was 18.12 ± 2.176 IU ([95% CI 13.6 to -22.4]) and was 11.66 ± 4.180 IU ([95% CI 3.5 to 19.6]) in group 2. At the end of the study, the subjects required nearly twice as much daily insulin with 70/30 than with glargine plus OAD (62.54vs. 32.02IU). However, the insulin dose increment from the baseline was more in group 1 compared to group 2.

Change in HbA1c over 12 months:

The change in HbA1c over the 12 months in both the groups is shown in the table 3. Over the course of the study, HbA1c (Mean ± SE) declined in both groups (figure 1). The change in HbA1C is as follows: At the baseline, the HbA1c was 10.76 ± 0.18 and 10.56±0.19 for group 1 and group 2 respectively. At the first Visit [third month] (group 1: 9.37±0.16%; group 2: 9.1±0.19%; p=0.29), at the second visit [sixth month] (group 1: 8.61±0.18%; group 2: 8.33±0.16%; p=0.27), at the third visit [ninth month] (group 1: 8.67±0.18%; group 2: 8.2±0.16%; p=0.47) and at the fourth visit visit [twelfth month] (group 1: 8.44±0.17%; group 2: 8.07±0.14%; p=0.09). Decrement in HbA1c was nearly same in both groups.

Table 2: Major findings of the study groups:

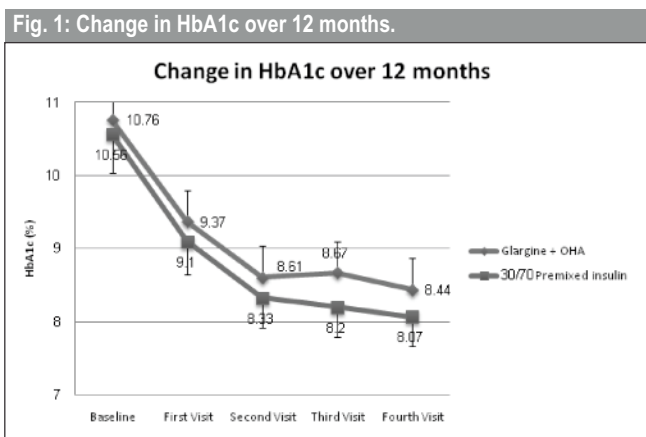
Parameters	Regimen	First	Last	Mean Difference	P
Changes in HbA1c	Glargine+ OAD	10.76±1.5	8.44±1.38	2.316 ± 0.25	< 0.0001
	70/30	10.56±1.55	8.07±1.21	2.489 ± 0.24	< 0.0001
Changes in FBG	Glargine+ OAD	209.8±6.1	138.9 ± 5.52	54.68 ± 17.93	< 0.0001
	70/30	208.8 ± 7.4	140.2 ± 5.4	68.57 ± 9.178	< 0.0001
Changes in Weight	Glargine+ OAD	76.71 ± 1.7	80.31 ± 1.7	3.597 ± 2.4	0.1394
	70/30	78.72 ± 2.1	83.25 ± 2	4.531 ± 2.9	0.1252
Changes in BMI	Glargine+ OAD	29.67±0.62	31.07±0.61	1.402 ± 0.88	0.1117
	70/30	31.07±0.86	32.82±0.82	1.758 ± 1.188	0.1413
Total daily insulin dose (U/day)	Glargine+ OAD	13.91±1.11	32.03±1.86	18.12 ± 2.176	< 0.0001
	70/30	50.89±2.66	62.54±3.22	11.66 ± 4.180	0.0060

Table 3: Change in HbA1c over 12 months:

Regimen	HbA1c Level (%)				
	Baseline	First Visit	Second Visit	Third Visit	Fourth Visit
2 OAD + Glargine	10.76±0.18	9.37±0.16	8.61±0.18	8.67±0.18	8.44±0.17
Premixed insulin 30/70 +metformin	10.56±0.19	9.1±0.19	8.33±0.16	8.2±0.16	8.07±0.14
P value	0.45	0.29	0.27	0.47	0.09

Table 4: Number of patients affected by hypoglycemic events.

Parameter	Regimen	Number	percentage
Hypoglycemia	Glargine+ OAD	10	14.7
	70/30	14	20



Hypoglycemia:

14 patients (20.6%) receiving glargine plus OAD and 10 patients(14.3%) receiving premixed 70/30experienced at least one hypoglycemic event (table 4). None of the patients required hospital admission for these episodes. Hypoglycemia was mostly recorded to be related to incomppliance with life style. None of the patients had severe hypoglycemia. Hypoglycemia affected elderly patients slightly more (57.1 %) than the young patients (42.9%) in group 1, whereas Hypoglycemia affected young patients more (60 %) than the elderly patients (40%) in group 2.

DISCUSSION

The prevalence of type II diabetes mellitus is a common nowadays, and is responsible for excess morbidity and mortality, micro and macro vascular complications, and impaired quality of life. Recent UKPDS study and other studies have highlighted the significance of achieving tight glycemic control to prevent such complications.^{13,14,15}

Initial treatment should begin with diet, weight reduction and exercise, which can induce normoglycemia if compliance is optimal. Patients with persistent hyperglycemia are typically started on one or more oral hypoglycemic agents. Insulin has traditionally been used only if inadequate control persists

despite use of these drugs. The therapeutic options for patients who fail initial therapy with combination of oral hypoglycemic drugs are either to add insulin or to discontinue the drugs and switch to insulin. Part of the rationale for combining an oral hypoglycemic drug with insulin therapy is that insulin can suppress hepatic glucose output, the primary cause of fasting hyperglycemia.¹⁶

This study assessed two approaches for initiating insulin therapy in poorly controlled type 2 diabetic patients who have failed to achieve target glycemic control goals on OHA therapy. The results showed that, in poorly controlled type II diabetes patients who are on oral therapy, stopping OHAs and starting twice-daily premixed 70/30 insulin can provide more effective glycemic control than adding a single injection of insulin glargine to a combination of oral hypoglycemic agents. The reductions in HbA1c provided a clinical improvement for subjects in the premixed 70/30 group, allowing significantly more 70/30 treated subjects to achieve HbA1c targets established by the American Diabetes Association.

The results of this study were comparable to a similar study where insulin therapy was initiated with either twice- daily biphasic insulin lispro 75/25 or once-daily glargine, both taken concomitantly with metformin (17). Reduction in HbA1c was greater in the lispro premix group, and more subjects reached target HbA1c ≤ 7% in 16 weeks when treated with lispro premix than with glargine (41 vs. 22%, *P* ≤ 0.001).

In another study, therapy with once-daily glargine plus sulfonylureas and metformin was compared with twice-daily biphasic human insulin premix alone, without OHAs.¹⁸ Although greater HbA1c reduction was observed in the glargine group at 24 weeks, the human premix group may have been disadvantaged by the removal of OHAs from the therapeutic regimen, specifically metformin, which has been shown to be very efficacious when used in combination with insulin therapy.¹⁹

In our study, the 70/30 insulin regimen enabled 31.4% of patients to reach HbA1c ≤ 7% without experiencing nocturnal hypoglycemia, whereas 26.5% of patients on glargine plus OHA achieved target HbA1c ≤ 7% in the absence of nocturnal hypoglycemia.

The events of hypoglycemia increase obviously when patients use insulin to achieve better glycemic control and defined glycemic targets. It is obvious that the overall incidence of minor hypoglycemia would be greater in the 70/30 group than in the glargine group considering that the 70/30 group had better glycemic control than the glargine group. Importantly, hypoglycemia was not a barrier to achieving glycemic targets for the 70/30 group. Studies show that increased risk of hypoglycemia is associated with intensive glycemic control using insulin²⁰, all the patients who are initiated with insulin therapy should always be referred to diabetes self management training programs to help them prevent, recognize, and manage their hypoglycemic episodes.

Initiation of insulin therapy is often accompanied by an increase in weight as glycemic control improves. The weight gain was more in 70/30 group in comparison with the glargine group, which is consistent with similar previous studies in both the treatment groups.^{21,22,23,24} The reason for the reduced weight gain with the glargine group may be the addition of metformin as a concomitant therapy, as reported by the previous studies.²⁵

Since patients randomized to the 70/30 group did not receive any OHAs, this study compared two regimens for initiating insulin rather than two specific forms of insulin. However, previous studies using NPH insulin in combination with OHAs showed lower weight gain in comparison to insulin monotherapy with premixed insulin.²⁶

In clinical practice, OHAs are often discontinued once a 70/30 insulin regimen is begun, but continuing metformin might be expected to improve the effectiveness of this regimen. Clearly, many questions remain regarding the initiation of insulin therapy in patients with type 2 diabetes. The current study provides efficacy and safety data pertaining to two commonly used insulin regimens. Further studies are required to provide physicians with additional guidance. These should include addressing the benefit of 70/30 insulin plus metformin combination to ascertain the level of influence of metformin on the results obtained in the insulin glargine-treated group.

In addition, it would be of interest to compare the glargine plus OHA regimen with a rapid acting analog plus NPH insulin as use of the latter insulin regimen becomes more widespread. The relative costs of treatment with all of these regimens, including the glucose testing required by each, should also be studied. Finally, despite the improvement in control achieved by 70/30 insulin regimen, over Three quarters of patients in the 70/30 group did not reach HbA1c \leq 7%.

Insulin therapy is typically begun only after lifestyle modification and OHA therapy fail to normalize HbA1c

values. In general, most individuals with type II diabetes rarely are started on insulin with HbA1c values \geq 8.5%. Unfortunately, many subjects will have had type II diabetes for 10–15 years before diagnosis and may have already developed complications (27). Therefore, earlier introduction of the most effective insulin therapy should be encouraged despite the reluctance of patients and their physicians.²⁸

Based on the results of this study, premixed 70/30 regimen appears to be more effective than insulin glargine + OHA and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type II diabetes that is not optimally controlled on OHA therapy.

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