

TRIPLE ORAL ANTIDIABETIC OR METFORMIN-BASAL INSULIN COMBINATION: TESTING TWO DIFFERENT APPROACHES OF CONSENSUS ALGORITHM IN ADJUSTING ANTIDIABETIC THERAPY. AN OPEN-LABEL, RANDOMIZED STUDY

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Abstract

Objective. The aim of this study was to compare the clinical effects of a triple oral antidiabetic combination *versus* basal insulin and metformin combination treatment in patients with poorly controlled type 2 diabetes.

Methods. Eighty patients with type 2 diabetes, who were treated by metformin and sulphonylurea combination, and had HbA1c values between 7.5 and 10 % (58 and 86 mmol/L), were randomized into two groups. The first group was given triple oral antidiabetic therapy (pioglitazone, metformin, and sulphonylurea) and the second group was given metformin and a bedtime basal insulin (insulin detemir) combination for 12 weeks. Metabolic parameters were evaluated.

Results. The mean fasting plasma glucose and HbA1c levels decreased in both groups. The decrease in HbA1c was slightly higher in triple oral antidiabetic group (p=0.046). The patients in triple oral combination group gained 0.2 kg (p=0.881) and those in the metformin-insulin detemir

combination group lost 1.7 kg (p=0.001) in 12 weeks (p=0.29 between groups). The frequency of hypoglycemia was higher in triple oral antidiabetic group (11 vs. 2 episodes, respectively).

Conclusion. Both sulphonylurea-metformin-pioglitazone and insulin detemir-metformin therapies provided significant improvements in glycemic control. However, sulphonylurea, pioglitazone and metformin combination led to more frequent hypoglycemic events, and weight management seemed in favor of insulin detemir-metformin combination.

Key words: Type 2 diabetes, treatment algorithm, combination, basal insulin.

INTRODUCTION

Intensified treatment strategies have been demonstrated to reduce the diabetes related complications in patients with type 2 diabetes (1-3). The

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American Diabetes Association (ADA) suggests that the HbA1c level should be kept below 7% (53 mmol/L) in order to prevent the development of complications (4). According to the diabetes treatment algorithm, if the HbA1c value remains above 7% (53mmol/L) despite the dual oral anti-diabetics (OAD) treatment, addition of a third OAD or basal insulin is recommended (5). In this project, clinical efficacy of a triple OAD combination was compared with a basal insulin plus metformin combination treatment in patients with poorly controlled type 2 diabetes, who were on dual OAD treatment.

PATIENTS AND METHODS

Our study was conducted on 80 patients over 18 years of age, who attended the Ministry of Health, Goztepe Training and Research Hospital Diabetes Clinic, and whose HbA1C values remained in the range of ≥ 7.5 - 10% (58 and 86 mmol/L) (despite receiving sulphonylurea plus metformin combination at effective treatment dosage at least for the last 3 months and who agreed to participate in the study. Existence of conditions essentially requiring the use of insulin, risks associated with the use of either insulin or OADs, any intestinal disorder affecting the absorption, active liver disease, renal failure and alcohol addiction were the exclusion criteria. The study protocol was approved by the Local Ethics Committee. (Approval Date 27.11.2007 and Resolution No: 41/1).

Demographic data and anthropometric and biochemical measurements were recorded. The

patients were randomized into two groups (1:1 ratio randomization). Patients were randomized group A and B according to their order of admission). In the first group, pioglitazone 15 mg daily was added on the metformin and sulphonylurea combination. In the second group, the sulphonylurea was stopped and insulin detemir (10 units once daily) was added on metformin therapy. Recommendations for intensified life style modifications were the same in both groups. In order to help them to reach their ideal weight, patients were introduced a refined carbohydrate restricted diet. The characteristic aspect of this diet was the total exclusion of flours and sugar. Only 60 g of daily consumption of bread was allowed (3 thin slices of bread). No other foods containing refined carbohydrates were allowed except that. Beside this, 30 min. walking was recommended as a daily exercise (6). The primary end point was the reduction rate in HbA1c, and secondary end points were to determine alterations in fasting plasma glucose, BMI values and hypoglycemia rates.

For glycemic control the values recommended by ADA were set as target (4). Patients were asked to perform self blood glucose monitoring 4 times a day at home until blood glucose was stabilized even at occasional measurements, and subsequently they were asked to measure the blood glucose once a day, except for the specific requirements (with Roche diagnostic-Accucheck active). Patients were invited for follow up visits weekly during the first month, and then at the end of 2nd and 3rd months. Insulin and/or OAD doses have been adjusted according to blood glucose values. The initial insulin doses were adjusted according to their lowest fasting plasma glucose levels; FPG < 120 mg/dL (6.6

mmol/L): no change, FPG=120-160 mg/dL (6.6-8.8 mmol/L): +2 U, FPG=160-180 mg/dL (8.8-9.9 mmol/L): +3 U, FPG=180-220 mg/dL (9.9-12.2 mmol/L): +4 U, FPG \geq 220 mg/dL (12.2 mmol/L); +6 U. After initial adjustments, insulin doses were increased or decreased 2 units according to their lowest blood glucose levels. Pioglitazone doses increased monthly, if lowest FPG \geq 120 mg/dL (6.6 mmol/L) without hypoglycemic attack history, because both groups were advised for strict life style modifications). Hypoglycemic attacks were defined as plasma glucose levels less than 70 mg/dL (3.8 mmol/L) or existence of hypoglycemic symptoms. On each visit, patients in both groups were told about the lifestyle changes, and their treatments were reemphasized. At the 12th week of randomization the clinical and laboratory measurements were repeated.

Statistical analysis

In statistical evaluation, all analyses were performed with SPSS-15.0 software. Variance between groups was compared by Student's t test, whereas within-group matched variables were compared by paired-samples T test. Data were expressed as means \pm SD. A p value below 0.05 (two tailed) was considered to be statistically significant.

RESULTS

Of the 80 patients enrolled in the study, 6 patients dropped out and the rest of the 74 patients completed the study. All the drop-outs participants were from the insulin plus metformin group (5 subjects discontinued receiving insulin because they changed

their minds about performing injection, and one subject could not be contacted).

The initial demographic and clinical data were similar among the patient groups (Table 1). At the end of the third month, pioglitazone dose in the first group was raised by 5 mg on average, and in the second group insulin detemir dose was increased by 6 units on average. In the first group, the mean daily total doses were 48.9 \pm 14.9 mg for gliclazide, 2.8 \pm 1.9 mg for glimepride, 20.1 \pm 10.6 mg for pioglitazone, and 1817.5 \pm 498.0 mg for metformin. In the second group, the daily total doses were 16 \pm 6.9 units for insulin detemir and 1762.4 \pm 556.3 mg for metformin. The percentage of patients that reached the target (HbA1c \geq 7 %) was 32.5 % in group A and 20 % in group B (p=0.24). The mean fasting plasma glucose and HbA1c levels were 151.5 mg/dL (8.4 mmol/L) and 7.6% (60 mmol/L) in the first group, whereas 157.2 mg/dL (8.7 mmol/L) and 8.1% (65 mmol/L) in the second group. The decrease in HbA1c levels (Δ HbA1c) was higher in the triple OAD group than in the insulin detemir plus metformin group (1.2 % (10 mmol/L) vs. 0.8 % (15 mmol/L) respectively, p=0.046; Table 2). The average blood glucose values of the patients in both groups throughout the three months observation period is shown in Figure 1. There was a significant (1.7 kg) weight loss (p=0.001) in the insulin detemir plus metformin group with respect to the start up conditions. Weight gain of 0.2 kg detected in the triple OAD group was not statistically significant (p=0.881; Table 2).

In this present study, hypoglycemic events were reported as 11 events in triple OAD group and 2 events in the other study group. No serious hypoglycemic event was

Table 1. Demographic and clinical data of the patients

	^a Group 1	^b Group 2	P
N	40	34	
Age (years)	58.5±9.44	59.8±12.25	0.564
Diabetes History (years)	9.6± 8.42	10.68±7.75	0.565
Body weight (kg)	78.64±11.35	80.02±13.21	0.739
BMI (kg/m ²)	30.21±4.29	31.185±5.55	0.338
FPG (mg/dL)	183.37±43.67	198.59±55.17	0.176
FPG (mmol/L)	10.18±2.42	11.03±3.06	0.176
HbA1c (%)	8.75±0.89	8.91±1.00	0.456
HbA1c (mmol/mol)	72±14	74±12	0.456

^aGroup 1: Patients receiving metformin-sulphonylurea-pioglitazone.

^bGroup 2: Patients receiving insulin-detemir.

Table 2. Comparison of the efficacy of the treatments

	Group 1			Group 2			ΔGroup1	ΔGroup2	p
	first	last	p	first	last	P			
Body weight (kg)	78.64	78.84	0.881	80.02	78.28	0.001*	0.20	-1.74	0.298
FPG(mg/dL)	183.37	151.50	0.001*	198.59	157.24	<0.001*	31.87	41.35	0.589
FPG (mmol/L)	10.18	8.41	0.001*	11.03	8.73	<0.001*	-1.77	-2.29	0.589
HbA1c(%)	8.75	7.46	0.001*	8.91	8.10	0.001*	-1.29	-0.81	0.046*
HbA1c(mmol/mol)	72	58	0.001*	74	65	0.001*	-9	-15	0.046*

Group 1: Patients receiving metformin-sulphonylurea-pioglitazone.

Group 2: Patients receiving metformin-insulin-detemir.

FPG:Fasting plasma glucose

observed in any groups. The mean blood glucose levels measured during the hypoglycemic events were 60.1±7.7 mg/dL (3.3±0.4 mmol/L) in group 1; and 58.5±4.9 mg/dL (3.2±0.2 mmol/L) in group 2 (p=0.79).

DISCUSSION

The results of this study showed a significant additional decrease in the

HbA1c levels of the patients receiving metformin and sulphonylurea, with either a triple OAD regimen with addition of pioglitazone, or insulin detemir plus metformin with initiation of a basal insulin.

Although the decrease in the HbA1c level in triple OAD group was slightly higher than that of the metformin basal insulin group, a trend to more hypoglycemic episodes has been observed in this group. Moreover,

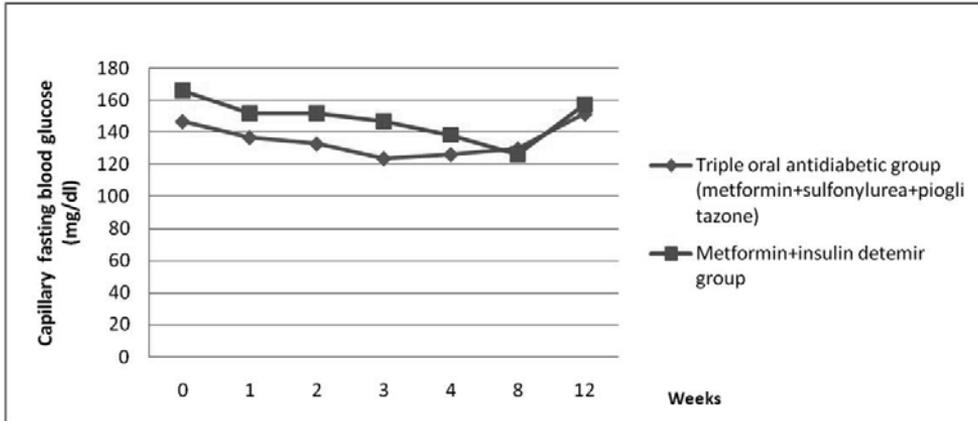


Figure 1. Glycemic alternations observed in the two different therapies.

*Follow up visits were performed every week during the first month, then once a month

the body weights of the patients were increased with this regimen, despite the intensive recommendations on life style modifications. The increase in detemir dose was modest during the study (only 6 IU). The total dose of detemir was of only 16 IU at the end of the 3 months. This could explain the better glycemic control with three oral drugs, the loss of weight with insulin therapy and the lower number of hypoglycemic events with insulin, as compared to oral drugs.

The addition of a third OAD is a widely recognized approach where the glycemic targets are not reached in patients receiving metformin and sulphonylurea combination. This approach has been tested in numerous studies in the literature (7, 8). However, in the studies conducted to date, it has been preferred to compare the triple OAD administration with the addition of insulin to dual OAD treatment (9-11). Our preference of insulin addition to metformin, while discontinuing the sulphonylurea in the second group may be accepted as challenging, but we believe that it is less rational to continue an insulin secretagogue agent in a setting where insulin is added on OAD

treatment. While opposite practices are being widely applied, there are also many authors in favor of this argument (12, 13). Another intriguing fact about the results of this study is that the two different approaches suggested for the second phase of the second step of this new algorithm are exactly concurrent with our therapy groups. Thus, this study was the first research where two different approach suggestions of this new algorithm in the treatment of type 2 diabetes have been tested in clinical practice.

In the study of Aljabri *et al.*, adding pioglitazone or bedtime NPH insulin for 16 weeks in patients who were receiving maximal doses of metformin and sulphonylurea, improved the glycemic control in type 2 diabetic patients. In contrast to our study, they reported more hypoglycemia by the addition of NPH insulin (13). In this study, the frequent occurrence of hypoglycemia in the group where basal insulin is added can be attributed to the continuation of sulphonylurea in these patients. In our study, the addition of insulin detemir in the second group to metformin as basal

insulin which has posed a lower hypoglycemia risk compared to NPH and discontinuation of sulphonylurea treatment can explain the less frequent occurrence of hypoglycemia.

In addition to hypoglycemia, weight gain is also one of the major challenges in maintaining a good glycaemic regulation. In our study, all patients were recommended an intensified life style modification program intended to weight loss. As a result of this program, 2% loss of body weight has been achieved in the metformin plus insulin detemir treatment group. Here, the discontinuation of sulphonylurea treatment may also have an impact as well as the changes in the life style. As a matter of fact, weight loss could not be achieved in patients using sulphonylurea and glitazone in their triple OAD combination. In two studies comparing the addition of either rosiglitazone or insulin glargine for patients receiving metformin and sulphonylurea treatment, both therapies were shown to reduce the HbA1c levels in comparable rates, while the weight gain of rosiglitazone patients were found to be higher than that of the insulin glargine group (10,14).

Recently two trials, Action in Diabetes and Vascular Disease-Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT) have shown no significant reduction in cardiovascular outcomes with intensive glycaemic control (15,16). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was halted in February 2008, due to the finding of an increased rate of mortality in the intensive glycaemic control arm compared with the standard glycaemic control arm. The intensive arm reached

a median A1c of 6.4% (46 mmol/L) within 12 months of randomization, while the standard group reached a median A1c of 7.5% (58 mmol/L) from a baseline median A1c of 8.1% (65 mmol/L) (17). Interestingly, the intensive glycaemic control group had more weight gain, and more episodes of severe hypoglycemia than the standard group. We believe that these results should not be interpreted as evidence against lower HbA1c targets, but as very important data to avoid antidiabetic regimens leading more hypoglycemia and weight gain.

Our study also had some limitations. One of the limitations was the three months study duration. It is obvious that a longer period would provide more reliable results to assess the effects of the antidiabetic treatment. Nevertheless, the fact that HbA1c value reached at the end of the 3rd month was also maintained at the end of the one year period in 4 T Study (18) suggests that the decrease in HbA1c value attained in our study at the end of the three months term can also be noteworthy. In this study, although the final fasting blood glucose and HbA1c levels have been decreased significantly during the study period, they were already higher than the levels recommended in the guidelines. Consequently, it was not possible to clearly determine the individual impact of life style modifications and the different treatment protocols introduced for glycaemic control and weight management. Considering the relatively small dose increments in pioglitazone and insulin treatment throughout the study, the reduction rate attained in HbA1c values (0.8%) in three months terms, which is comparable to the results of other studies, can be attributed to the intensive life style intervention

program that was introduced for both groups since decrease in insulin sensitivity is the main problem in type 2 diabetes (19, 20). Pioglitazone treatment has known one of the most effective therapy choices increase insulin sensitivity (21). Nevertheless, the present study showed that their addition to sulphonylureas can cause more frequent hypoglycemic attacks.

In conclusion, in this study we observed that both the triple OAD therapy with metformin, sulphonylurea and pioglitazone combination, and the treatment with metformin plus basal insulin combination can provide significant additional decrease in HbA1c levels in patients, whose glycemic control could not be maintained with dual OAD treatment with metformin and sulphonylurea. However, the administration of sulphonylurea and glitazone causes more frequent hypoglycemic events, and attenuates the efficacy of life style modifications on weight management compared to addition of insulin detemir to metformin.

Conflict of interest.

The authors did not report any conflict of interest.

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