COMPARISON OF BASAL INSULIN ADDED TO ORAL AGENTS VERSUS TWICE – DAILY PREMIXED INSULIN AS INITIAL INSULIN THERAPY FOR TYPE 2 DIABETES

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ABSTRACT:

Objective: To compare the efficacy and safety of adding once – daily basal Glargine insulin versus switching to twice – daily premixed insulin in Type-II diabetic patients not well controlled by combined oral antidiabetic agents.

Methods: In a 6 months parallel group clinical trail on 221 patients with Type-II diabetes and poorly controlled on oral antidiabetic agents (fasting blood glucose > 140 mg/ dl and glycosylated hemoglobin >8%) on oral antidiabetic treatment (metformin plus sulfonylurea) were randomized either to add Glargine insulin or to shift them to mixed insulin (30% regular insulin and 70% NPH) twice per day without oral antidiabetic treatment. Insulin dosage was titrated to target fasting blood glucose < 100 mg/dl and predinner blood glucose < 120 mg /dl.

Results: Mean hemoglobin A_1C decrease from baseline was significantly pronounced (- 2.1 vs. - 1.3 % p = <0.005), and more patients reached HbA_1C <7% (57 vs. 31%) with Glargine insulin plus oral antidiabetic treatment than with mixed insulin. The number of patients who achieved the target of fasting blood glucose < 100 mg/dl were more in the group which received Glargine insulin than the other group that received mixed insulin (41.7 vs. 17.8 %).

Conclusions: Initiation of insulin therapy in patients with Type-II diabetes uncontrolled on combined metformin and sulfonylurea by adding Glargine insulin was more effective than starting with twice daily of mixed insulin (30% regular insulin and 70% NPH insulin).

KEYWORDS: Type-II diabetes, insulin, Glargine insulin.

INTRODUCTION

Treatment of patients with Type-II diabetes mellitus includes education, exercise, diet control and medication. The medication available for treatment of Type-II diabetes stimulate beta cell to secret insulin or these drugs increase the sensitivity of the insulin. The optimal level of glycemic control in patients with Type-II diabetes is becoming clear. The United Kingdom Prospective Study of diabetes demonstrated that near normal blood glucose concentrations markedly reduce the microvascular complication.[1] 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.[2] Most of the patients with Type-II diabetes failed to achieve the glycemic goals by diet, exercise, and combined oral antidiabetic agents. They need either addition or shifting them to exogenous insulin, for better glycemic control. We used to shift them to twice daily mixed insulin but after availability of Glargine insulin we started to added it to the combined oral antidiabetic agents. The objective of this study was to find the efficacy of adding Glargine insulin to Type-II diabetes insufficiently controlled by oral agents in comparisons to twice daily mixed insulin.

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PATIENTS AND METHODS

Two hundred and twenty one patients diagnosed to have Type-II diabetes and inadequately controlled by combined oral antidiabetic agents were included in the study. They were treated by maximum dose of metformin and sulfonylureas for at least 3 months. They were followed at the endocrinology clinic at Dr Soliaman Fageeh Hospital (DSFH), in Jeddah city Saudia Arabia. DSFH is one of the biggest private hospitals in Jeddah city. It is very busy hospital with more than 350 beds. The out patients endocrine clinic in DSFH is very busy clinic with more than 40 patients daily. We applied the ADA standard care of diabetes, and aimed to achieve their recommended goals in treatment of diabetes. Fasting blood glucose, postprandial blood glucose, fasting serum lipids, and glycosylated hemoglobin was done in all our patients suffering from diabetes and repeated in follow up. The patients included in our study were having glycosylated hemoglobin more than 8% and fasting blood glucose more than 140 mg/dl. They were continuously followed up and agreed to be included in the study. The patients weltering from chronic renal failure, severe cardiac disease and elderly patients (age >70 years), were excluded from the study. They were divided into two groups. In one group Glargine insulin was added while patients in the other group were put on mixed insulin (30% regular insulin and 70% NPH). The starting dose of Glargine insulin was 14 units per day titrated up weekly according to the fasting blood glucose levels. Fasting blood glucose was more than 200 mg/dl. The dose was increased by 8 units. In case of less than 200 and more than 140 mg/dl the dose was increased by 4 units per week. The doses of mixed insulin were one unit per kg in the beginning divided to two third in the morning and one third in the evening. The morning dose was increased weekly by 4 units if the postprandial level was more than 200 mg/dl and the evening dose was increased by 4 units if the fasting blood glucose was more than 140 mg/dl. They were followed weekly in the first month then monthly for a total of six months. In each visit, fasting blood glucose and postprandial blood glucose were obtained. The vital signs, neurological examination, cardiovascular examination and the weight were documented every month. The glycosylated hemoglobin and serum lipids profiles were done in the beginning and then after every 3 months. SSPP 10 was used for data analysis.

RESULTS

A total of 221 patents were included in this study and all completed the six month follow up. There age was from 43 – 70 years (56.3). It included 97 female and 124 male. One hundred and eleven patients received Glargine insulin in addition to the combined oral antidiabetic drugs, while 110 patients were shifted completely to mixed insulin. The highest dose of Glargine insulin given was 60 units, with mean dose 40 units. In mixed insulin we increased the dose up to 120 units (mean 60 units). The fasting blood glucose before Glargine insulin were more than140 with mean 187 mg/dl but after treatment it was between 95 – 155mg/dl with mean 103 mg/dl. Eighty three patients achieved the required fasting blood sugar. The glycosylated hemoglobin before Glargine insulin was 8 – 16.4% with mean 11.4% and after treatment it decreased to 8.7%. Patients treated with mixed insulin showed improvement of blood glucose from the mean level of 183 to 133mg/dl, and the glycosylated hemoglobin improved from 11.2% to 9.8%. The mean glycosylated hemoglobin reduced by 2.7% in patients treated by Glargine insulin and in patients treated by mixed insulin by 1.4% (p-value < 0.005).

Mean weight of patient in both groups was 67.3 kg and it increased after treatments. In Glargine insulin group the mean weight increased by 3.4 kg, whereas in the other group, it increased by 7.3 kg. (p-value = <0.005).

DISCUSSION

Based upon the results of UKPSD, normoglycemia is now the goal for many, if not most of the patients with Type-II diabetes.

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 hypoglycemics. 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.[3] Data from the UKPDS and meta-analysis of several randomized placebo – controlled trails of combination therapy reveal modest but consistent benefits of combination therapy compared with insulin monotherapy.[4-6] Combination therapy was associated with reductions in glycosylated hemoglobin from 11.2 percent pretreatment to 10.1 percent, and in fasting blood glucose concentrations from 210 to 167 mg/dl.[4]

Similar findings with nighttime NPH insulin (ie, equivalent glycemic control with or no weight gain compared to several daily insulin injections) have been described in other studies of patients inadequately controlled with drugs alone.[7-11]

In patients who are not well controlled on two oral agents, switching them to insulin may be more effective than adding a third oral agent. Patients on three oral agents (a sulfonylureas, metformin, and glitazone) had poorer glycemic control, more side effects, a more atherogenic profile, and higher costs than patients on twice daily insulin along with metformin.[12]

Glargine insulin can be used instead of NPH insulin, at bed time in addition to oral antihyperglycemic drugs. It has no peak action, which make it good as basal insulin in intensive insulin treatment. It may be equally effective as NPH insulin in reducing glycosylated hemoglobin value and may cause

slightly less nocturnal hypoglycemia, albeit at greater cost.[13] The optimal timing of once – daily NPH is at bed time, while morning administration of insulin Glargine appears to be better.[14]

Insulin can also be given as monotherapy without continuation of oral drugs. This approach is cheaper than combined therapy but results in more weight gain and more episodes of hypoglycemia.[1] Adding Glargine insulin once daily to combined oral antiglycemic agents was safer and more effective than beginning twice daily injections and discontinuation oral antihyperglycemic drugs.[15] Our study showed similar result as regards efficacy of Glargine insulin with oral antiglycemic drugs than twice daily mixed insulin.

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