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Original Article

Comparison of Effectiveness of Insulin Glargine in Combination with Oral Hypoglycemic Agents Versus Continued Premixed Insulin in Indian Type II Diabetes Patients: Randomized Controlled Trial

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ABSTRACT

Background and Objectives: The development of novel insulin analogs and the availability of glucose-lowering medications revolutionized the diabetes therapy protocol. The aim was to compare the efficacy and therapeutic outcome of daily insulin glargine alongside oral hypoglycemic agents and premixed human insulin in Type II diabetes priorly receiving conventional insulin therapy. **Materials and Methods:** This was a sixteen-week, single center, parallel randomized controlled trial. The study included participants with Type II DM who had poor glycemic control and were currently on premixed human insulin. The patients were randomized into three groups, where A received insulin glargine, B received insulin glargine, glimepiride and metformin and C were instructed to continue their previous treatment with addition of premixed insulin. The blood was collected to measure the therapeutic efficacy and all adverse events were recorded. **Results:** The study comprised of 185 patients and HbA_{1c} dropped by 0.63%, 0.73% and 0.53% in group A, B and C respectively, whereas intergroup analysis did not show statistical significance. There was a significant reduction in mean fasting blood glucose levels from baseline to endpoint in every group (p=0.003; 0.014; 0.036). There were no notable significant adverse events occurred in any of the groups. **Conclusion:** Insulin glargine combined with glimepiride alone or with metformin serves as an efficient alternative therapy for individuals with Type II Diabetes Mellitus who failed to achieve adequate management on prior ongoing therapy with premixed insulin.

Keywords: Insulin Glargine, Diabetes Mellitus, Oral Hypoglycemic Agents, Combination Therapy.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic condition marked by high blood sugar levels brought on by insufficient insulin secretion (Type-1) or resistance (Type-2), it can have grave repercussions if left untreated. An all-too- of poorly managed diabetes over time inflicts significant damage on several of the body's organ systems, particularly affecting the blood vessels and neurons. About 25 million Indians over the age of 18 are prediabetics, or at a higher risk of acquiring diabetes in the near future, while an estimated 77 million have type 2 diabetes.[1] Type 2 DM is primarily characterized by Insulin resistance. This leads to the adaptation of beta-cells in the pancreas by releasing more insulin and increasing the cell mass which initially results in hyperinsulinemia. However, it sets off a vicious loop that results in beta cell deterioration and escalates the need for insulin even in insulin-resistant diabetes.[2]

Up until the development of basal insulin analogs and the availability of novel glucose-lowering medications, insulin NPH was the ideal basal insulin therapy. NPH was then combined with metformin and/or sulfonylureas to define the standard of care.[3] As newer insulin analogues with different pharmacokinetic profile became available, patients were prescribed long-acting insulin to maintain ideal levels of fasting blood glucose and if needed even short acting analogues were added to manage and avoid sudden spike in post-prandial glucose.[4] The well-known long-acting insulin analogs are glargine and detemir. A single daily shot of insulin glargine maintains a basal insulin level throughout the course of the day.[5] This study aimed to compare the effectiveness

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and therapeutic outcomes of daily insulin glargine in combination with two oral antihyperglycemic agents versus pre-mixed human insulin in Type II DM patients previously treated with conventional insulin therapy.

MATERIALS AND METHODS

This was a prospective randomized controlled trial which was structured into two distinct phases: a four-week run-in phase and a sixteen-week therapeutic phase. The study's inclusion criteria comprised of individuals with Type II DM who had suboptimal glycemic control defined by HbA_{1c} of 8.0% or higher and FBS greater than 120 mg/dL and were currently on premixed human insulin i.e., two injections of 25/75 of regular insulin and NPH insulin. Impaired liver and kidney function, pregnancy, mental illness that prevents the patient from understanding the purpose, extent and potential outcomes of the trial, or incapacity to complete the follow-up appointments were excluded from the study.

Baseline involved documenting the patient's whole medical history, performing a physical assessment and going over the admission requirements. A fasting blood sample was taken for the test to estimate the levels of serum C-peptide, creatinine, aspartate aminotransferase, alanine aminotransferase and HbA_{1c}. Prior to study treatment, the participant's body weight and height were recorded. During the study's run-in phase, all individuals were advised to adhere to their regular premixed insulin regimen. Additionally, an insulin dosage adjustment was made to reach the target FBG of less than 121 mg/dL.

The patients were divided into three groups. In Group A, participants were administered insulin glargine once daily before breakfast, accompanied by a daily dose of 3 mg glimepiride. The initial dose of insulin glargine matched the previous dosage of NPH insulin used in premixed insulin therapy. Meanwhile, Group B received a combination therapy consisting of insulin glargine, glimepiride and metformin. Metformin treatment commenced at 500 mg twice daily and was gradually titrated up to a maximum of 850 mg twice daily as required. Patients in group C were instructed to continue their previous treatment plan in addition to adding 75/25 or 70/20 premixed human insulin. During the treatment period, the dose of insulin was changed whenever feasible to achieve the FBG goal value of less than 99 mg/dL. On the aforementioned weeks 1, 2, 4, 8, 12 and 16, the patients visited the study site before breakfast. Blood was taken to test for FBG, liver enzymes and serum creatinine during the patients' visit on scheduled weeks.

Examining the injection site and calculating the amount of insulin were the techniques used to assess the patient's compliance. Patients were advised to carry study medications, used insulin cartridges and any additional empty cartridges to every appointment. The level of HbA_{1c} was evaluated at baseline, week 11 and at the endpoint. The patients were instructed to measure FBG levels daily in order to self-monitor blood glucose.

The FBG levels were analyzed using the daily glucometer values that patients measure at 7 a.m., in addition to the FBG values that are derived from laboratory values at 4 weeks (run-in phase), week 0 of randomization and week 16 of the study. At the terminal of the study, all patients were asked to fill out a questionnaire aimed at evaluating their satisfaction with the treatment regimen. The summed score was calculated by adding the scores for items 1 and 4-8. Item 2 (high glucose values) and 3 (low glucose values) were examined separately. Each questionnaire item had a score between 0 and 6, so the overall score for treatment satisfaction could be anywhere between 0 and 36 points.[6] Patients were asked to document any hypoglycemic episodes, blood glucose of 60 mg/dL), with or without symptoms. Adverse events were defined as any unanticipated health events connected to study-related exams or medications.

Statistical Analysis: SPSS was used for data assessment and statistical analysis. Data review and analysis planning were done prior to database closure, regardless of treatment assignment. Baseline and endpoint evaluations of the primary efficacious variable (HbA_{1c}) were analyzed on an Intent-to-Treat (ITT) basis. A two-sided test at the 5% level was used to conduct hypothesis statistical testing. There was no multiple comparison adjustment made. All of the data is expressed as mean+SD and $p \leq 0.05$ was considered to be statistically significant.

RESULTS

The study screened 191 patients, where four individuals in Group C dropped from the trial prior to Visit 11 following randomization, stating gastrointestinal problems as their cause for discontinuation and two from Group A (Figure 1). As a result, 185 individuals made up the ITT group, which consisted of all participants who had evaluations for the key efficacy contingent, HbA_{1c}, at baseline (week 4) and week 16. Table 1 summarizes medical and biochemistry features of each group at baseline. The results showed no substantial variations in mean duration of diabetes, the length of insulin treatment, C-peptide scales, FBG figures, or HbA_{1c} between Group A, B or C, despite the fact that the participants in Group C were considerably older compared to those in other groups.

At the endpoint, HbA_{1c} dropped in Group A by 0.63±0.49% to 8.01±0.63% with p of 0.024 and in Group B by 0.73±0.93% to 7.42±0.81% with p=0.004 from baseline. HbA_{1c} levels in Group C tended to decline from baseline by 0.53±0.96% to 7.54±1.21% at endpoint, p=0.043, with no statistically significant distinction between the groups.

Table 2 provides a summary of the mean FBG levels shift trend from baseline to endpoint. It was discovered that each group's improvement from starting to completion was statistically

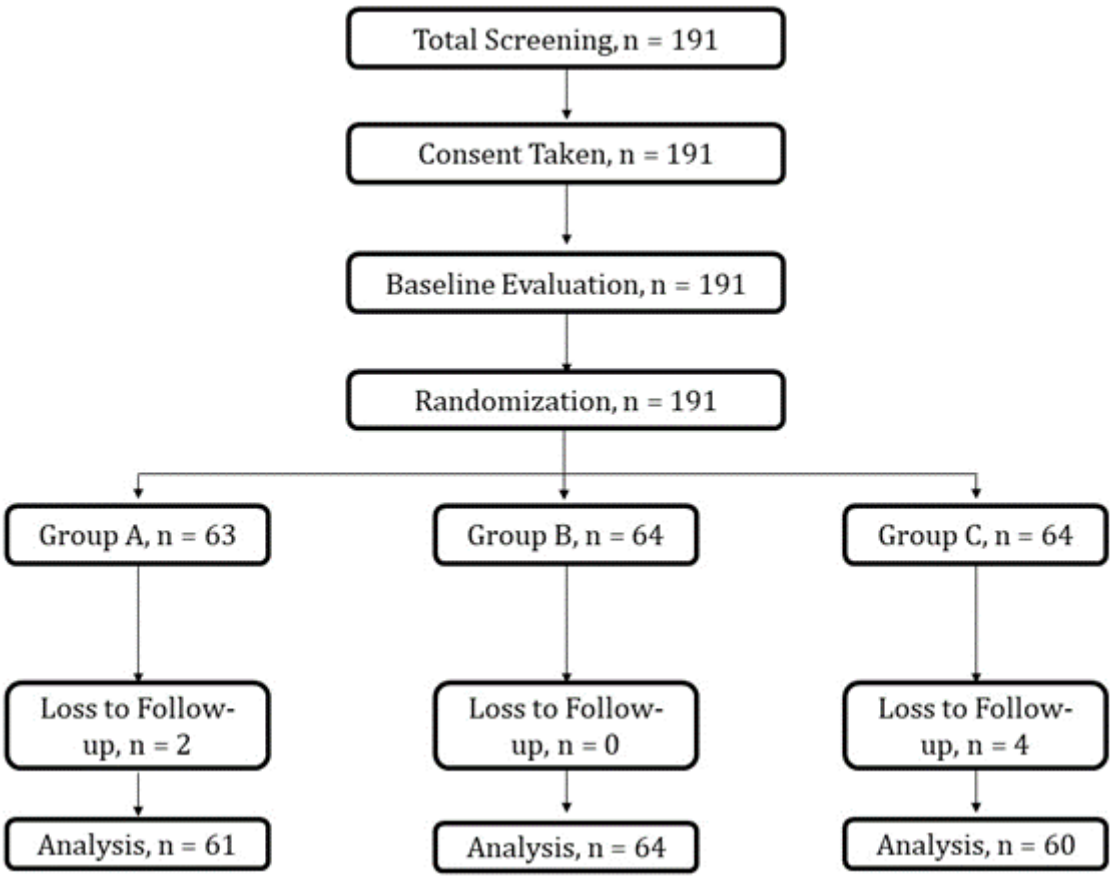

Figure 1: Flow of Participants in the trial.

Table 1: Baseline Clinical and Biochemical Characteristics of the Study Participants.

	Group A	Group B	Group C
Number, n	61	64	60
Age in years, Mean±SD.	57.18+12.7	63.7+9.7	68.3+8.4
Diabetes duration, in years, Mean±SD.	14.3+7.3	13.6+9.30	17.3+5.3
Duration of insulin therapy in years, Mean±SD.	4.3+2.9	3.7+2.9	3.8+1.9
Body weight in Kg, Mean±SD.	87.6+19.6	86+12.3	91+12.9
BMI in kg/m^2, Mean±SD.	33.7+2.8	31.9+1.9	30.2+1.4
C-peptide in nmol/L, Mean±SD.	3.2+2.0	2.9+2.9	2.7+1.8
Insulin dose, IU/day, Mean±SD.	77.7+27.9	73.5+37.8	69.7+39.7
HbA_{1c} in %, Mean±SD.	8.64+0.76	8.15+0.66	8.07+0.97
SGOT in IU/L, Mean±SD.	32.31+8.78	41.30+9.79	33.26+9.83
SGPT in IU/L, Mean±SD.	36.41+10.33	39.34+11.43	31.29+8.07
Creatinine in mg/dL, Mean±SD.	0.97+0.8	0.83+0.91	0.9+0.12
Systolic blood pressure in mmHg, Mean±SD.	147.9±28.7	143.7±22.1	152.8+23.9
Diastolic blood pressure in mmHg, Mean±SD.	77.9+11.9	85.3+12.3	76.9+9.3

Table 2: Mean Change of FBG from Baseline to Endpoint in Study Participants.

Study Groups	Baseline Mean+SD	Endpoint Mean+SD	*p* Value
Group A, mg/dL	169+36	125+ 39	0.003
Group B, mg/dL	173+73	129+41	0.014
Group C, mg/dL	162+63	131+28	0.036

substantial. Intergroup comparison, however, did not show statistical significance, suggesting that each group's therapeutic efficacy for lowering FBG is consistent. In spite of this, blood sugar readings at the endpoint were considerably lower in each of the three groups compared to baseline.

All three research groups received identical baseline insulin dosages. The mean insulin dosage rose in Group C to 71.3±42.7 IU/day with p=0.018, sank in Group B to 49.8±27.7 IU/day with p=0.017 and endured fairly constant in Group A i.e., at baseline of 77.7+27.9 IU/day and 76.7±34.2 IU/day at endpoint indicating p of 0.638. Nonetheless, the statistically noteworthy difference among the groups was not found. Throughout the trial, every patient in Group B was receiving the highest permitted dosage of metformin (1700 mg/day). While there was a trend for BMI and body weight to rise among individuals in Group A, these parameters weren't affected in Groups B or C from baseline to endpoint. Group A's BMI increased by+0.43 kg/m2 to 34.13±3.1 kg/m2 at the end of the trial. During the trial, there were notable but statistically insignificant changes in body weight.

The therapy satisfaction evaluation revealed that all participants were satisfied with their medical care. All three treatment groups had comparable treatment satisfaction scores at the endpoint. Groups A, B and C showed mean scores of 33.6+6.3, 31.9+6.2 and 33.4+5.3, respectively. There was no substantial change in treatment satisfaction across the therapy groups.

Safety Analysis

There were no incidents of severe hypoglycemia that requiring intravenous glucose therapy over the 16-week trial period. In Group A, 63% of patients experienced at least one mild hypoglycemia episode; in Group B, the ratio was 67%; and in Group C, it was 53%. Additionally, there were no variations in the overall frequency of mild hypoglycemia events experienced by any patient. In all three therapy groups, blood pressure, serum creatinine and hepatic enzymes did not alter from baseline.

There were no clinically noteworthy aberrant test results in any of the three groups throughout the trial period. With the exception of diarrhea and gastrointestinal distress, there were no treatment-emergent adverse events observed in the study. Patients in Group B reported to have adverse effect more frequently. Additionally, as previously indicated, 2 out of 64 patients in this group had their therapy discontinued three weeks post allocation because of gastrointestinal issues. Once premixed insulin was resumed, the gastrointestinal issues resolved.

DISCUSSION

Oral Hypoglycemic Agents (OHAs) are typically the initial course of action in the treatment plan for individuals with Type II diabetes when adjustments to lifestyle are no longer adequate to maintain optimal glycemic control. In the long run, insulin treatment is necessary for many patients either to replace or enhance the effects of OHAs. According to all standards, if lifestyle modifications and oral medications fail to reach glycemic objectives, insulin (basal, premixed, or other formulations) should be initiated. In the past ten years, it has been advised to start insulin treatment immediately when blood sugar levels are ≥300 mg/dL or glycated hemoglobin levels are greater than 10%.[7] Insulin administration can be embarked in patients utilizing basal insulin, pre-prandial insulin, or twice-daily premixed insulin, either individually or in conjunction with pre-prandial insulin.[8] Patients should engage in organized therapy and educational programmed as part of both treatment approaches.[9,10]

For patients with Type II diabetes who do not respond to OHA therapy, a straightforward regimen consisting of long-acting insulin and OHA therapy can be implemented in lieu of premixed insulin. It has been demonstrated that individuals who shift from OHA alone to the aforementioned strategy, maintains adequate glycemic control.[11,12] The objective of the present investigation was to determine if it would be feasible and beneficial for older patients who were not responding to twice-daily premixed insulin to transition to once-daily dawn injections of insulin glargine in addition to OHAs.

This study demonstrated that baseline HbA_{1c} levels were akin as well as that all three therapy groups produced equivalent metabolic regulation (HbA_{1c}) at end. Furthermore, FBG levels were similar across all three treatment groups from baseline to endpoint. The insulin glargine groups, but not the premixed insulin group, showed a substantial baseline to endpoint surge in glycemic control after implementing a preset titration protocol to the equivalent blood glucose objectives. While prior research on patients with Type I and Type II DM has shown that the use of insulin glargine substantially decreases the likelihood of low blood sugar when compared to NPH insulin,[13,14] this investigation differs from the others as insulin glargine was juxtaposed with NPH insulin instead of NPH insulin as part of a premixed

regimen. The adoption of alternative FBG titration goals may account for the lower incidence of hypoglycemia bouts.

The WHO asserts that the best diabetes control is attained with a HbA_{1c} of less than 6.5% and an FBG of less than 120 mg/dL.[15] Nevertheless, neither group in the current investigation's HbA_{1c} reached the WHO criteria. This makes reasonable since the period of follow-up was just 16 weeks, which is a limited time frame to monitor the suggested modifications. There are records indicating that the administration of insulin glargine with metformin plus glimepiride caused the study participants' HbA_{1c} level to drop below 6.5%.[16,17] In addition, the titration schedule employed in this study could not have been ideal because the patients had been using insulin for around 4 years prior. it could be an indication of the comparatively low incidence of hypoglycemia seen in all three research groups during the investigation. On the other hand, considerable individuals in long-term trials reported hypoglycemia due to either insulin alone or in conjunction with OHA.[18,19] For this reason, it is advised that patients who have been treated with insulin monotherapy for a long period need to follow a more rigorous titration protocol.[20] The findings indicate that individuals with inadequate glucose control, defined as HbA_{1c}>8.0% on regular premixed insulin treatment, might benefit greater from the use of insulin glargine plus one or more OHAs or advancing up to a greater degree of insulin administration protocol than remaining on their current course of treatment.

CONCLUSION

Insulin glargine combined with glimepiride alone or with metformin serves as an efficient alternative therapy for individuals with Type II Diabetes Mellitus who failed to achieve adequate management on prior ongoing therapy with premixed insulin. Additionally, the significant percentage of patients who articulated an intent to continue receiving insulin glargine therapy at the completion of the study indicates that individuals endorse this course of care as well as that it is an appropriate option for patients who might reconsider receiving regular or premixed insulin therapy.

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ABBREVIATIONS

HbA_{1c}: Glycated Hemoglobin; **DM:** Diabetes Mellitus; **NPH:** Neutral Protamine Hagedorn; **FBG:** Fasting Blood Glucose; **SPSS:** Statistical Package for Social Sciences; **ITT:** Intent-To-Treat; **SD:** Standard Deviation; **BMI:** Body Mass Index; **SGOT:** Serum glutamic oxaloacetic transaminase; **SGOT:** Serum glutamate pyruvate transaminase; **OHAs:** Oral hypoglycemic agents; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

The institutional Ethics Committee clearance has been obtained prior to the conduct of study. Informed consent has been taken from each patient of participation.

AUTHORS CONTRIBUTIONS

Akankchha Verma: Conceptualization, Methodology, Investigation, Resources; Aditya V: Writing-Original Draft, Writing-Review and Editing; Girish B S: Formal Analysis, Data Curation, Writing-Original Draft, Writing-Review and Editing; Kiran Nagaraju: Supervision

SUMMARY

In this prospective randomized controlled trial involving 185 participants with Type II diabetes and suboptimal glycemic control, three treatment groups were evaluated over a 16-week period. Group A received daily insulin glargine with glimepiride, Group B received insulin glargine with glimepiride and metformin and Group C continued on premixed human insulin therapy. The primary endpoint, HbA_{1c} levels, improved significantly in all groups from baseline, with no statistically significant differences observed between groups. Insulin dosage adjustments varied among groups, with Group B requiring the highest metformin doses and Group C showing increased insulin requirements. Patient satisfaction with treatment was high across all groups and safety profiles indicated no severe hypoglycemic events, although mild hypoglycemia was reported similarly among groups. Adverse events were mostly gastrointestinal, predominantly in Group B, highlighting the need for monitoring and management during treatment. Overall, the study demonstrates comparable efficacy and safety profiles among the treatment regimens evaluated, suggesting that individualized approaches may optimize management of Type II diabetes based on patient response and tolerability.

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