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Comparative Study of NPH Insulin with Glargine in Patients of Type 2 Diabetes Mellitus Poorly Controlled With Oral Hypoglycaemic Agents.

Baljinder Singh Bal[1], Surinder Kumar Salwan[2], Ashok Duggal[3], Mohammed Umar Farooq[4]

[1]Professor and Head, Dept. of Medicine, Government Medical College, Amritsar
[2]Assistant Professor, Dept. of Medicine, Government Medical College, Amritsar
[3]Associate Professor, Dept. of Medicine, Government Medical College, Amritsar
[4]Resident, Dept. Of Medicine, Government Medical College, Amritsar.

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ABSTRACT

Background: Type 2 Diabetes Mellitus is an emerging pandemic with number of patients increasing rapidly in both developed and developing nations. In patients with secondary failure of type 2 diabetes after oral hypoglycaemic agents (OHAs), Insulin is the treatment, which is available in various forms with respect to viable duration of action. Basal Insulins or background insulins are used commonly either alone or with short acting insulins. NPH insulin is intermediate acting insulin given once or twice daily whereas Glargine is long acting insulin given once daily. **Methods:** In this study, 120 patients of type 2 diabetes mellitus already on oral hypoglycaemic agents who were not optimally controlled with combination of 2 or 3 oral hypoglycaemic agents were included after excluding patients of Type 1 diabetes, gestational diabetes and those who were newly diagnosed or already on insulin therapy. Patients were divided into 2 groups of 60 patients each. Group A were put on NPH insulin and Group B on Glargine insulin for 12 weeks. Along with parameters of diabetes and side effects were compared with special reference to early morning hypoglycaemia (at 3 am).**Results:** Mean reduction in fasting blood glucose was 54.42 mg/dl in Group A as compared to 66.62 mg/dl in Group B, which was statistically significant with a p value < 0.0001. Regarding hypoglycaemia it was seen in 31.67% in Group A vs. 11.67% in Group B and was significant (p=0.0078). Nocturnal hypoglycaemia was also seen to be more in Group A than Group B with values of 21.67% and 5% respectively, which was significant. There was no significant difference in daily dose requirement. **Conclusion:** This study showed that Insulin Glargine was better than Insulin NPH in terms of glycemic control and less side effects with respect to hypoglycemic events and nocturnal hypoglycemia with no significant difference in daily dose requirements.

Keywords: Glargine, Glycemic control, Nocturnal hypoglycaemia, NPH insulin, Type 2 Diabetes mellitus.

INTRODUCTION

Insulin has been an indispensable part of diabetes management since its discovery. Insulin has gone through various modifications, with the currently available range of insulin having a little resemblance to the brown crystalline powder produced in 1921. The currently available insulins can be classified as broadly as rapid-acting, premixed, or intermediate /long acting. All these can be of human or analog origin.[1]

Name & Address of Corresponding Author
Dr. Surinder Kumar Salwan
Assistant Professor,
Dept of Medicine,
Government Medical College, Amritsar.

Majority of patients with a longer duration of diabetes remain poorly controlled with oral agents, and use of insulin, which could improve glycemic control, is often long delayed and not aggressive enough. The reluctance to initiate insulin therapy seems partly due to its perceived complexity, and fear of hypoglycemia, which may be the greatest barrier.[2]

The UKPDS highlighted the importance of glycemic control in preventing long-term complications associated with T2DM. This study reported that even a 1% reduction in HbA_{1C} would decrease significantly the risk of deaths associated with T2DM by 21%, myocardial infarction by 14%, and microvascular complications by 37%.[3] One of the most alarming consequences of the diabetes upsurge is the appearance of type 2 diabetes in children and adolescents. Until the end of 20th century (or millennium), type 2 diabetes mellitus was regarded as a disease of the middle aged and elderly. Although it is still true that this age group maintains a higher relative risk, there is accumulating and disturbing evidence that onset in the 20-30 years of age group is rising alarmingly.[4,5]

Acknowledging the impetus of Diabetes mellitus in all age groups with emerging picture of younger age group and the occurrence of its varied complications warrants a study to earmark the insulin type most suitable for its treatment. So the present study was conducted to compare the safety and efficacy of the long-acting insulin Glargine and NPH insulin in patients with type 2 diabetes mellitus who were previously treated with oral hypoglycemic agents alone but inadequately controlled.

MATERIALS AND METHODS

This was an open labeled prospective single centered study. This study was done on 120 patients of type 2 diabetes mellitus already on oral hypoglycemic drugs, but not optimally controlled fulfilling the inclusive as well as exclusive criteria, attending the outdoor departments or admitted in various wards of the Guru Nanak Dev Hospital attached to Government Medical College, Amritsar.

Inclusion criteria:

1. Patients who are known cases of type 2 diabetes mellitus already on combination of two or three oral hypoglycemic drugs but not optimally controlled

Exclusion criteria:

1. New onset type 2 diabetes mellitus
2. Type 1 diabetes mellitus
3. Gestational diabetes mellitus
4. Those already on insulin therapy

After selecting the subjects fulfilling the above mentioned criteria, their informed and written consent was taken for their participation in the study. Detailed history was taken regarding presenting complaints, symptoms of type 2 diabetes mellitus, its duration and complications and treatment. Personal history was taken especially for dietary habits, alcohol consumption, smoking, exercise or any other addiction. General physical examination was done and specifically for height and weight. Patients were thoroughly examined to look for the signs suggestive of micro-vascular or macro-vascular complications and findings were recorded as per the Performa.

Routine investigation was performed with complete blood counts, renal function tests, liver function tests, thyroid function tests, electrocardiography etc. to know the general condition of the patient and to rule out renal, cardiac or hepatic disease.

All patients were investigated for fasting blood glucose levels, blood glucose levels at 3 am, $HbA1_C$ from venous blood samples.

Patients were divided into 2 groups:

GROUP A: Patient on NPH insulin: 60 patients

GROUP B: Patient on insulin Glargine: 60 patients

All patients were trained for the self-monitoring of the fasting blood glucose levels every 2 weeks and to inform the same through telephonic conversation. Any symptoms related to the hypoglycemia were explained to all patients and for self-checking the blood glucose levels and reporting the same either through telephone or through personal visit.

All the baseline parameters were repeated after 12 weeks and independent sample 't' test was applied to mean values of fasting blood glucose, $HbA1_C$, body weight of both the groups to find out whether the difference was statistically significant or not. The difference was considered statistically significant when the result was $p< 0.05$.

RESULTS

This prospective study was an open label, single center study conducted on 120 patients to compare the efficacy of NPH insulin versus Glargine on fasting blood glucose levels, $HbA1_C$ reduction in type 2 diabetes mellitus patients poorly controlled on oral hypoglycaemic agents, their effects on body weight and nocturnal hypoglycaemia assessed after 12 weeks of treatment.

Of 120 patients of type 2 diabetes mellitus already on oral hypoglycaemic drugs, but not optimally controlled were selected. All patients were ambulatory and were haemodynamically stable. Patients were divided into two groups, Group A and Group B. Patients in group A were put on NPH insulin 10-20 units depending upon the fasting blood glucose levels:

- <150 mg/dl= 10 units at night
- 151-170 mg/dl= 12 units at night
- 171-190 mg/dl= 14 units at night
- >190 mg/dl= 16 units at night

Patients in Group B were put on Insulin Glargine 8-20 units depending upon fasting blood glucose levels:

- ≤140 mg/dl= 8 units at night
- 141-150 mg/dl= 10 units at night
- 151-170 mg/dl= 12 units at night
- 171-190 mg/dl= 14 units at night
- >190 mg/dl= 16 units at night

Dose of the insulin was increased or decreased to obtain the desired FBS levels as per the guidelines.

Table 1: Biochemical results of the study groups.

Parameter	Time Of Measurement	Group A (NPH Insulin) Mean ± SD	Group B (Glargine) Mean ± SD	P Value
Body weight (kg)	**At Baseline**	70.92±7.82	71.92±10.49	0.5550
	At 12 weeks	72.36±7.83	72.32±10.19	0.9808
Fasting Blood glucose (mg/dl)	**At Baseline**	178.58±46.87	192.33±38.86	0.0828

	At 12 weeks	124.17±36.79	125.72±29.21	0.7987
Frequency of documented hypoglycemia	**At 12 weeks**	19	7	0.0078
Frequency of patients with nocturnal hypoglycemia	**At 12 weeks**	13	3	0.0072
HbA_{1C} (%)	**At Baseline**	8.17±0.80	8.04±0.78	0.2409
	At 12 weeks	7.51±0.71	7.07±0.53	0.0002
Insulin requirement (u/day)	**At Baseline**	12.97±2.54	13.73±2.25	0.0854
	At 12 weeks	16.30±3.33	16.23±3.32	0.9142

Table 2: Comparison of Mean Body Weight gain in study groups.

Groups	No. of Patients	Mean gain in Body weight (Kgs)	SD	P Value
Group A (NPH)	60	1.44	0.87	<0.0001
Group B (Glargine)	60	0.41	1.10	

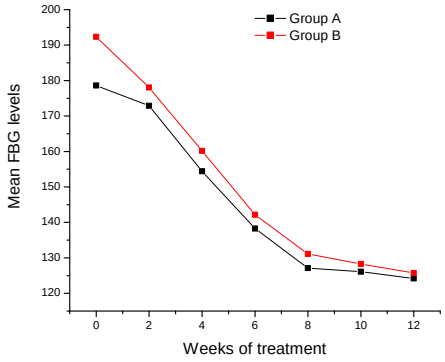

Figure 1: Mean Fasting Blood glucose levels every two weeks from baseline in both the groups.

DISCUSSION

Insulin Glargine is a human insulin analogue prepared by recombinant DNA technology. Modification of the human insulin molecule at position A21 and at the C-terminus of the B-chain results in the formation of a stable compound that is soluble at pH 4.0, but forms amorphous micro precipitates in subcutaneous tissue from which small amounts of insulin glargine are gradually released. The plasma concentration versus time profile of insulin glargine is therefore relatively constant in relation to conventional human insulins, with no pronounced peak over 24 hours. This allows once-daily administration as basal therapy.[6] The absorption characteristics of insulin glargine are not affected by the site of injection (arm, leg or abdominal regions). Also, compared to NPH insulin, the absorption rate is significantly slower with approximately 50% of the injected dose of insulin glargine still detectable after 24 hours compared with approximately 20% of the NPH insulin dose.[7]

The mean body weight after 12 weeks of treatment was 72.36 ± 7.83 kgs in Group A while for Group B it was 72.32 ± 10.19 kgs. For this, the p value was 0.9808, which was statistically insignificant. But the average gain in body weight after 12 weeks of treatment was 1.44 kgs in Group A as compared to 0.41 kgs in Group B which was statistically extremely significant (0.0001). [Table 2] A 28 weeks study by Rosenstock J et al.[8] comparing insulin Glargine and NPH insulin in type 2 diabetes patients found that subjects in Glargine group experienced less weight gain than those in the NPH group (0.4 vs 1.4 kg, p< 0.0007) which is comparable with the findings our study.

After 12 weeks of treatment, the mean fasting blood glucose levels were similar in both the groups (124.17 ± 36.79 vs 125.72 ± 29.21, p= 0.7987). Also the number of patients achieving the target fasting blood glucose levels of < 130 mg/dl were similar in both the groups (32 vs. 37, p= 0.356) but the mean reduction in the fasting blood glucose levels from baseline was significantly higher in Glargine group as compared to NPH group (66.62 vs 54.42 mg/dl, p< 0.0001). In a study by Fulcher GR et al[9] in patients with type 1 diabetes mellitus wherein the mean baseline FBG were similar for the glargine and NPH groups (11.2 vs 11.4 mmol/L). The means for end-point FBG were 7.9 versus 9.0 mmol/L. Adjusted LSM change from baseline was -3.46 versus -2.34 mmol/L, with significant difference of 1.12 mmol/L in favour of glargine (P< 0.05). In another study by Hershon et al.[10] in patients with type 1 diabetes mellitus after 28 weeks of treatment, FBG level reduction was 1.17 vs 0.56 mmol/dl (p=0.02) from baseline in Glargine vs NPH insulin group. In another study in type 1 diabetes mellitus by Raskin et al.[11] after 16 weeks of treatment echoed similar results. FBS reduction from baseline to endpoint was 1.7 vs 0.6 mmol/dl in favour of Glargine group as compared to NPH group (0.0001). In 28 week study carried out in children by Schober et al.[12] it was found that FBG reduction of 1.29 mmol/dl in Glargine group as compared to 0.68 mmol/dl reduction in the NPH (p=0.02).

As shown in [Table 1] in this study, number and percentage of patients with documented hypoglycemia i.e. FBS levels < 72 mg/dl was significant lower in Glargine group as compared to NPH group(7[11.67%] vs 19{31.67]). In a study by Riddle et al.[13] found that 13.9% of subjects in Glargine group and 17.7% in NPH group experienced hypoglycemia which was statistically significant (0.02). Rosenstock et al.[8] also ;found

similar lower rate of hypoglycemia in Glargine group as compared to NPH group (61.4% vs 66.8%, p<0.05). Similarly a study by Yki-Jarvinen et al. [14] also found lower rates of hypoglycemia with glargine group as compared to NPH group(33% vs 42%, p=0.04). A study in patients with type 1 diabetes mellitus by Ratner et al.[15] found that frequency of hypoglycemia was significantly lower in Glargine group as compared to NPH group (39.9% vs 49.2%, p<0.05). Similarly another study by Hershon et al.[10] in type 1 diabetes patients also found that frequency of hypoglycemia was significantly lower in Glargine group as compared to NPH group (73.3% vs 81.7%, p=0.02).

After 12 weeks of treatment, number and percentage of patients with documented nocturnal hypoglycemia (<72 mg/dl) i.e. blood glucose levels at 3 am, was 13 (21.67%) in NPH group as compared to 3 (5%) in Glargine group, p value being 0.0072 which was statistically significant. A study by Massi Benedetti et al.[16] observed that frequency of nocturnal hypoglycemia was significantly lower in Glargine group as compared to NPH group (9.5% vs 22.2%, p< 0.0006). Another study by Eliaschewitz et al.[17] also demonstrated lower frequency of nocturnal hypoglycemia in Glargine group as compared to NPH group (20.4% vs 34.8%, p< 0.001). Study by Riddle et al.[13] also found similar lower rates of nocturnal hypoglycemia in Glargine group as compared to NPH group (4%vs 6.9%, p< 0.001). In patients with type 1 diabetes mellitus study by Ratner et al.[15] found that the frequency of nocturnal hypoglycemia was significantly lower in Glargine group as compared to NPH group (18.25 vs 27.1%, p< 0.05).

As shown in the [Table 1] in this study, mean ± SD of $HbA1_C$ after 12 weeks of treatment in Group A was 7.51± 0.53% for which p was statistically significant (0.0002). In a study by Pan et al.[18] after 24 weeks of treatment in patients with type 2 diabetes mellitus $HbA1_C$ change from baseline to endpoint in Glargine group was -0.99% as compared to -0.77% in NPH group which was statistically significant (p=0.032). In another study by Yki-Jarvinen et al.[14] in patient with type 2 diabetes mellitus demonstrated significant reduction in $HbA1_C$ in Glargine group as compared to NPH group (p<0.001). In a study by Fulcher GR et al.[9] in patients with type 1 diabetes mellitus demonstrated significant reduction in $HbA1_C$ in Glargine group as compared to NPH group (-1.04 vs -0.52% with p < 0.01). In a study by Arushi Saini et al.[19] in type 1 diabetes mellitus demonstrated significant reduction in $HbA1_C$ levels in Glargine group as compared to NPH insulin group (7.44 vs 8.89%, p<0.001)

The number of patients achieving the desired $HbA1_C$ goal of <7% was 31(51.67%) in Group B as compared to 22(36.67%) patients in Group A which was statistically insignificant (p< 0.0980). In a study by Riddle et al.[13] demonstrated that the percentage of patients achieving $HbA1_C$ goal were 58% vs 57.3% in Glargine vs NPH group which was statistically insignificant (p=NS).

The mean ± SD of total daily insulin requirement of insulin at baseline was 12.97 ± 2.54 U/day in group A and 13.73 ± 2.25 U/day in group B, p value being 0.0854 which was statistically insignificant. After end of 12 weeks Insulin requirement for glycemic control was 16.30 ± 3.77 U/day in group A and 16.23 ± 3.32 U/day in group B, p value was 0.9142 which was statistically insignificant. In a study by Pan et al.[18] insulin dose was 22 U in Glargine group and 23 U in NPH group, p value was not significant. In a study by Rosenstock et al.[8] insulin dose was 0.75 U/kg each in Glargine and NPH group, p value was not significant. Another study by Eliaschewitz et al.[17] insulin dose was 32.6 U in Glargine group and 31.2 U in NPH group, p value being not significant. Another study by Fritsche et al.[20] insulin dose was 37 U vs 39 U in Glargine vs NPH group which was not significant. Another study by Yki-Jarvinen et al.[14] also demonstrated no significant difference in insulin dose between the Glargine and NPH insulin subgroups (23U vs 21U).

CONCLUSION

The two important indicators of efficient diabetic treatment are: the tight glycemic control and minimal risk of hypoglycemia. Our study concluded that Insulin Glargine fits the bill for both the indicators and emerges as the more viable and reliable option for uncontrolled type 1 diabetes on oral hypoglycemic drugs. Average reduction in FBG levels from baseline, number of patients achieving desired FBG goal of < 130 mg/dl and number of patients achieving the desired $HbA1_C$ goal of < 7% was significantly better in glargine group as compared to NPH group. Insulin Glargine also reported less weight gain over the 12 weeks period as comparable to NPH insulin. This is a significant difference to propel patients to opt for Glargine. Its once-a-day dose improves compliance, gives an added advantage for better management of diabetes, and defers its long-term complications.

Thus from this study it is concluded that Insulin Glargine is better alternative to NPH Insulin in terms of glycemic control and few side effects with respect to hypoglycemic events, nocturnal hypoglycemia and weight gain with no significant difference in the daily dose requirements.

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