Original article:

Comparative study of insulin glargine and NPH insulin in poorly controlled type 2 diabetic patients on OHA

Dr. Anurag Prasad,* Dr. Muzaffari Yasmeen, Dr. Suchitra G Prasad,*** Dr. Md Rashid Taj****

*Associate Proffesor, Dept of Medicine, Rama Medical College Ghaziabad 245304(U.P)

** Assistant Proffesor, Rama Medical College Ghaziabad 245304(U.P)

*** Associate Proffesor, D.J Dental College Modinagar(U.P)

**** Assistant Proffesor, Rama Medical College Ghaziabad 245304(U.P)

Corresponding author : Dr. Md Rashid Taj

Abstract

Introduction: Diabetes mellitus is one of the most common endocrine disorders. Approximately 180 million individual worldwide have diabetes and by 2030 this number is expected to double. India has largest number of diabetics in the world with a prevalence of 2.4% in rural and 4-11.6% in urban population. Most diabetic patients are initially treated with OHA. Those who are poorly controlled on OHA are shifted to or combined with Insulin therapy to achieve good glycemic control.

Aims and objective: To compare the efficacy and the incidence of hypoglycemia with addition of Insulin Glargine vs. NPH insulin in Type 2 Diabetes mellitus patients poorly controlled on OHA.

Result and observation: Prior to initiating Insulin therapy mean value of HbA1c in group 1 and group 2 being 11.70$\pm$1.30 and 11.90 $\pm$1.64 respectively. Number of patients achieving good glycemic control in treatment group 1 was 8 (40%) of the 20 patients while only 6 patients (30%) achieved that level in NPH insulin group. The hypoglycemic events reported were higher in NPH insulin group as compared to Glargine Group. In Glargine Group Overall 12 patients reported to have hypoglycemic events (13 events) while 15 patients taking NPH insulin reported hypoglycaemic events (26 events).

Key words: Type 2 Diabetes Mellitus, Insulin Glargine, NPH Insulin

Introduction

Diabetes Mellitus is one of the most common endocrine disorders encountered in clinical practice. Diabetes was once regarded as a single disease entity but is now considered as a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly. The World Health Organization estimates that more than 180 billion people worldwide have diabetes and by 2030, this number will be doubled[1].India alone has largest number of diabetics in world with prevalence of 2.4% in rural and 4-11.6% in urban population[2] . Diabetes has been broadly classified as Type 1 and Type 2. Type 2 diabetes is 9 -10 times more prevalent than Type 1 diabetes mellitus.[3] The traditional approach for managing Diabetes includes dietary modification and exercise. [4] When these measures fail to control the blood sugar hypoglycemic agents like Sulphonylureas and insulin sensitizers like Biguanides or Thiazolidinediones are used.[5] These drugs may be used as a monotherapy or in combination with other oral hypoglycemic agents. The American Diabetes Association recommends that HbAlc concentrations should be lowered to less than 7%, fasting plasma glucose levels should be

maintained at 90 to 130 mg/dl.[6] It has been observed that patients using oral therapy seldom achieve and maintain the recommended <7% HbAlC goal for glycemic control and are exposed to increasing risks of diabetic complications.[7] As a result of the natural progression of Type 2 diabetes and loss of B-cell function, traditional treatment regimens incorporating oral agents often fail to help patients achieve these goals over the long term, exposing them to nocturnal hypoglycemia, and fasting and postprandial hyperglycemia.[8] Thus highlighting the fact that adequate basal insulin levels are an essential component of diabetes management. Based on available evidence and on clinical experience, a rational approach to treatment is to select an insulin regimen that would help patient to achieve the HbA1C target (<7.0%). Despite of insulin therapy being the most potent and durable hypoglycaemic intervention it has generally been saved for the last, presumably because of the need to administer it by injection.[9] Many different regimens of intensive insulin treatment have been developed and studied for their ability to provide better 24-hour glycemic control and to decrease the frequency and severity of long term complications. Three distinct treatment strategies with insulin have been tried to mimic the physiological insulin secretion by the body e.g. intermediate acting or long acting insulin plus oral hypoglycaemic agents, combination .intermediate acting insulin (e.g. NPH) or long acting insulin analogs (e.g. glargine) mimic the normal physiological basal insulin levels while short acting insulin mimic the surge of insulin in postprandial state. This study has focused and compares the efficacy with special reference to 24 hour of glycemic of control and safety of insulin glargine and NPH insulin combination with oral hypoglycemic agents in type 2 diabetes mellitus.

Aims and objective

To compare the efficacy and incidence of hypoglycemia of Insulin Glargine with NPH insulin in patients of Type 2 Diabetes mellitus inadequately controlled on oral hypoglycemic agents.

Methodology

The Study patients were recruited from the medicine outpatient department and diabetic clinic of Rama Medical College & Hospital during the period of April 2014 to September 2014. The patients attending the OPD were screened for the disease and a detailed and relevant present, past, personal, family and medical history was noted. It was followed by baseline laboratory investigations including hemogram, LFT, KFT, lipid profile and urine investigations to confirm and assess the diabetic status of the patient. Patients were trained to take insulin. Patients fulfilling all inclusion and exclusion criteria were enrolled in the study. They were allotted randomly in two treatment arms till 20 completed patients in each group, to receive either insulin glargine (Treatment Group 1) or NPH insulin (Treatment group 2), to be administered as subcutaneous injections at bedtime in thigh region. A written informed consent was obtained from all the subjects before their enrolment in study. They were asked to record the blood glucose levels twice weekly by glucometer, record the date wise dose of insulin administered and record any clinical adverse event during the period in the given diary cards. The starting dose of both insulin was 10 I.U. Efficacy was measured under following heading:

1. The change in (HbAIc) at baseline and at the end of study.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

2. Fasting blood glucose levels measured at base line, at every visit and at the end of study.
3. Twice weekly morning fasting b1ood glucose levels measured by glucometer by the patient himself.
4. Percentage of patient reaching HbAlC less than 7% without documented nocturnal hypoglycemia.
5. Requirement of titration of dosage of insulin and the final dose of insulin.

Result and observation

The study has been conducted in the Department of Medicine, RAMA Medical College & Hospital, Ghaziabad (Uttar Pradesh) during a period of January 2014to June 2014.

Subjects

A total of 135 patients were enrolled in the study, Of the 40 patients included in the study 20 were started on Insulin Glargine and 20 patients on NPH insulin in addition to pre study oral hypoglycaemic agents. There was no significant difference between groups with regards to demographics, diabetic disease characteristics, or metabolic control at baseline.

Table 1: Baseline Glycosylated Haemoglobin

	Treatment Group 1 (n=20)	Treatment Group 2 (n=20)	p value
Glycosylated Haemoglobin (%)			
<10	04	03	
10.1- 11	04	06	
11.1- 12	04	03	
12.1- 13	06	06	
>13	02	02	
Mean ± SD	11.70± 1.30	11.90 ± 1.64	0.61
Range (Min-Max)	8.1-14.3	8.3-13.9	

Glycosylated Hemoglobin: all the patients in both group have very poor glycemic control with mean value in group 1 and group 2 being 11.70± 1.30 and 11.90 ± 1.64 respectively. Table 1 show that the value of Glycosylated Haemoglobin ranges from 8.1-14.3 in group 1 and 8.3-13.9 in group 2

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Table 2: Fasting Blood glucose Pre and Post Treatment in two treatment groups

	Pre treatment	Post treatment	Mean difference	Pvalue
Treatment group 1	317.77 ± 71.89	113.70 ± 14.33	211 ± 72.93	0.00
Treatment group 2	323 .45 ± 78.59	119.85 ±11.84	196.60 ± 73.04	0.00

Mean fasting blood glucose level in Treatment group 1 was 317.77 ± 71.89 at the onset. A statistically significant decrease was observed at end of 4 and 8 weeks. At end of study the fasting blood glucose level fell to 113.70 ±14.33 which was statistically significant (p=0.00). In treatment in group 2 also there was a significant decrease in fasting blood glucose levels from baseline level of 323 .45 ± 78.59 to 119.85 ±11.84 at the end of study which was statistically significant (p=0.00).

Table 3: Comparative decrease in HbA1c value in two treatment group.

	Pre treatment	Post treatment	Mean difference	Pvalue
Treatment group 1	11.40 ± 1.56	7.50 ± 1.35	3.84± 1.56	0.00
Treatment group 2	11.86 ± 1.72	8.24 ± 1.61	3.33 ± 1.06	0.00

The insulin glargine and NPH groups had similar baseline. HbA1c levels 11.40 ± 1.56 % and 11.86 ± 1.72 %. The post treatment end point HbAIc values for insulin glargine and NPH insulin was 7.50 ± 1.35%and 8.24 ± 1.61 %, respectively. Reductions in HbAlc from baseline to end point in insulin glargine was 3.84± 1.56 % (p =0.00) and NPH insulin group was 3.33 ± 1.06 % (p=0.00).

Table 4: percentage of persons achieving therapeutic goal (HbA1c <7%) in two treatment groups.

	Treatment group 1	Treatment group 2	p Value
< 7% (good)	8 (40%)	5 (25%)	0.31
> 7% -< 7.5% (satisfactory)	4 (20%)	4 (20%)	
>7.5%- <8% (fair)	2 (10%)	1 (5%)	
>8% (poor)	6 (30%)	10 (50%)	0.19

Number of patients achieving good glycemic control in treatment group 1 was 8 (40%) of the 20 patients while only 6 patients (30%) achieved that level in NPH insulin group. The difference between the treatment groups was not significant (p=0.496).The number of patients who were still having a poor glycemic control (HbAlc>8%) were 10 in NPH group (50%) while the insulin Glargine group had only 6 patients (30%) who were not able to achieve a HbA1c level below 8% which was not statistically significant.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Table 5: Incidence of hypoglycemia in two treatment groups

Hypoglycemia	Treatment group 1		Treatment group 2		P value	F value
	Number of events	Mean SD	Number of events	Mean SD		
Nocturnal	1	0.05 ± 0.05	5	0.25 ± 0.19	0.08	3.23
Symptomatic	12	0.6 ± 0.25	18	0.9 ± 0.41	0.10	2.71
Severe	0	0	3	0.15 ± 0.24	0.17	1.87
Total	13	0.65 ± 0.34	26	1.3 ±1.58	0.04	4.36

The hypoglycemic events reported were higher in NPH insulin group as compared to Glargine Group. In Glargine Group Overall 12 patients reported to have hypoglycemic events (13 events) while 15 patients taking NPH insulin reported hypoglycaemic events (26 events). While there was no case of severe hypoglycaemic event in treatment group 1 there were events of severe hypoglycemia in treatment group 2, however the difference was not significant($p>0.05$).No severe hypoglycaemic episodes requiring treatment assistance from another person occurred. Number of symptomatic hypoglycemic events was higher (18 vs. 12) in NPH insulin group (Mean 0.9 ± 0.41) when compared to patients taking insulin Glargine group (Mean 0.6 ± 0.25) but not significantly different ($p>0.05$). Episodes of nocturnal hypoglycemia also were one (1) with insulin Glargine group (Mean 0.05 ± 0.05) as compared to five (5) in NPH insulin (Mean0.25 ± 0.19). The difference between the two episodes was not significant ($p >0.05$). The difference in total number of hypoglycaemic events in two groups was significant ($p<0.05$) with number of events being thirteen (13) in group 1(Mean 0.65 ± 0.34) while twenty six (26) in group 2 (Mean 1.3 ±1.58).

Table 6: Insulin dose requirement at the end of study in both groups

	Mean	Median value	Range (Min-Max)	P value
Treatment Group 1	32.80 ± 14.43	35	50 (12-62)	0.10
Treatment Group 2	37.90 ± 15.90	43	50 (14-64)	

All the patients in both groups were started on 10 IU. At study end point, subjects treated with insulin Glargine were receiving an average of 32.80 ± 14.43 IU basal insulin per day at bedtime. Subjects treated with NPH were receiving an average dose of 37.90 ± 15.90 IU basal insulin per day at bedtime. The difference between the end doses was not statistically significant ($p>0.05$). The median value of final insulin dosage was found to be 35 and 43 in group 1 and group 2, respectively.

Discussion

This open labeled, randomized, parallel, comparative study was designed in Indian population to confirm the finding of the studies carried out in western population. First, it was proof of concept testing the hypothesis whether supplementing oral therapy with the bedtime injection of basal insulin can routinely

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

achieve the recommended 7% HbA1c target in this population, maintenance of normal blood glucose level and its safety profile in terms of incidence hypoglycemia.. Second, it tested which of the two insulin, insulin glargine or NPH insulin, is better to provide this supplementation. In the present study both the treatment regimens effectively decreased the fasting blood glucose to the normal blood glucose levels (117 vs. 122 mg/dl). Our study findings concur with the findings of study done by Riddle MC et al (2003) who reported the mean fasting blood glucose at end point was similar with insulin glargine and NPH insulin (117 vs. 120 mg/dl).[10] The goal of HbAlc<7 % is set for most patients of diabetes and anything more than 8% indicates poor control of diabetes.[11] Thus measuring their levels prove to be an important criterion for clinical management, efficacy assessment and outcome of the treatment protocol. Both insulin regimens significantly reduced mean HbAlc levels of 3.84± 1.56 % and 3.33 ± 1.06 %% in insulin glargine and NPH insulin respectively from baseline value of 11.40 ± 1.56 % and 11.86 ± 1.72 % for insulin glargine group and NPH insulin group respectively to 7.50 ± 1.35%and 8.24 ± 1.61 % at end point. This is in accordance with the study reported by Yki-Jarvinen H et al (1999') both the insulin reduced the mean HbA1c level to 7.2 ±0.2 % (mean difference of-2.5 ± 0.4 %) at the end of 1 year. [12] 40% of patients on insulin glargine and 25% of patients on NPH insulin reached a target HbA1c level of 7% or less. However 50% of the patents in NPH insulin group had HbA1c levels of more than 8% at the end of study in comparison to 30% in group of patients taking insulin glargine. However in the study carried by Riddle MC et a1 (2003) over 60% patients achieved this target. This difference could be attributed to the higher baseline HbA1c level (11.3%) in our patients as compared to the other study (8.6%) and the treatment duration of our study which is comparatively shorter for achieving the targeted glycemic index compared to previous study.[10] This was similar to the observations made by Riddle MC et al. (2003) who reported that the mean deviation from the median of fasting values for individual subjects was greater with NPH than with Glargine (20.36 mg/dl vs. 18.38 mg/dl).[13] Overall 60% patients (12 out of 20) reported at least 1 episode of hypoglycemia in Glargine Group while 75% patients (15 out of 20) taking NPH insulin reported at least one episode of hypoglycemia. However the total number of hypoglycemic events was 50% less in treatment group 1 as compared to treatment group 2 (13 vs. 26). This was statistically significant ($p<0.05$). The mean number of hypoglycemic events per patient was 0.65 ±0.344 episodes per patient in Glargine group while NPH group had mean of 1.3±1.589 episodes per patient. Frequency of daytime hypoglycemia was significantly low with the insulin glargine group. Similar results have been reported by Yki-Jarvinen H et al. (2000) who have shown significant decrease in nocturnal hypoglycemia (9.9 vs.24.0 % of all patients, glargine vs. NPH, $P <0.001$) as also over all hypoglycemia.. In other studies, far lesser percentage of individuals on insulin glargine had nocturnal hypoglycemia as compared to patients taking NPH insulin. All the studies demonstrate comparable number of symptomatic hypoglycemic episodes in both the treatment group.[14, 15, 16]. An important aspect of treatment of diabetes is achieving the goal of <7 HbA1c level without any hypoglycemic episodes. More number of patients able to do so reflects a better compliance with such treatment protocol which will then show up as better treatment satisfaction levels as well as better sense of

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

well being and good perception of quality of life. In our study, although both insulin achieved similar FPG and HbA1c levels, insulin glargine did so with considerably less symptomatic hypoglycemia. 62.5 % of the patients achieving HbA1c < 7% had no episodes of hypoglycemia in treatment group 1 while only 50% were able to do so in treatment group 2 however the difference was not statistically significant (p>0.05). These data confirm the hypothesis that glargine is better suited as basal insulin regimen than NPH by allowing patients to reach recommended levels of glycemic control more safely. Similar results have been reported by Riddle Mc et a1 (2002) also found the similar result of achieved the target HbAlc level of 7% or less.[17] In our study, the average dose requirement of insulin glargine was 32.80 ± 3.23 which was less than the average dose of 37.90 ± 3.56 of NPH insulin. However, the difference was not significant for two groups (P>0-05). The average insulin dose requirement per kilogram body weight was 0.44 ± 0.04 and 0.53 ± 0.05 for insulin glargine and insulin NPH respectively. In Study done by Riddle MC eta1(2003) mean daily dosages at end point were 47.2 ± 1.3 I U for insulin glargine vs. 41.8 ± 1.3 for NPH (P<0.005; between-treatment difference5.3 IU [95% CI 1.8- 8.9]). Mean daily dosages at end point adjusted for body weight were 0.48 ± 0.01 IU/kg for glargine vs. 0.42 ± 0.01 IU/kg for NPH (P<0.001; between treatment difference 0.06 IU/kg [0.02-0.09]).

Conclusion

We have found in our study that the pre dinner blood glucose level was better controlled in patients taking insulin Glargine than the NPH insulin group. The overall dose requirement for insulin glargine was less as compare to NPH insulin, but the difference between the end doses was not statistically significant p was 0.10. The difference in total number of hypoglycaemic events in two groups was Significant (p<0.05) with number of events being 50% less episodes in glargine group.

References:

[1] . World Health Organization. Fact sheet: diabetes. No.312, http://www.who.int/mediacentre/factsheets/en/index.html.

[2] . Epidemiology of chronic non communicable disease and conditions, in Park K : Park's Textbook of preventive and social medicine. India M/S Banarsidas Bhanot, 18th

[3] . Sherwin RS. Diabetes mellitus, in Goldman L, Bennett JC (eds): Cecil EWtbook of Medicine. Philadelphia, WB Saunders, 2000, 1263-85

[4] . Prospective Diabetes Study (UKPDS) Group. UK Prospective Diabetes Study 11: Reduction in HbA]C with basal insulin supplement, sulfonylurea, bi guanide therapy in maturity-onset diabetes: a multi-center study. Diabetes.l985; 34:793-8.

[5] . Nathan DM, Initial management of glycemia in Type.2 Diabetes mellitus. N Engl J Med.2002; 147: 1342-9

[6] . American Diabetes Association. Clinical practice recommendations 2003. Diabetes Care. 2003;26(suppll):Sl-SlS6.

[7] . Turner RC, Cull CA, Frighi V, Holman RR. UK Prospective Diabetes Study Group: Glycemic control with diet, sulfonylurea, metformin, or insulin. JAMA. 1999; 281:2005- 12

[8] . Stratton 1M, Adler AI, Neil HA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405-11

[9] . Lepore M, Pampanelli S, Fanelli C, et al. Pharrnacokinetics and pharmacodynamics of subcutaneous injection of long acting human insulin analogue glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro; Diabetes. 2000; 49:2142-8.

[10] . Riddle MC, Rosenstock J, Gerich J. The treat to target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003; 26: 3080-6.

[11] .American Diabetes association. Standards of Medical care 2013. Final 21 Dec 2012 (1) ppt

[12] . Yki-Jarvinen H, Ryysy L, Nikkila K, Tuiokas T, Vanamo R, Heikkiia Comparison of bedtime insulin regimens in patients with type 2.diabetes mellitus . A randomized mntrolled trial. Ann Intern Med. l999;130:389.96

[13] . Yki-Jarvinen H, Dressler A, et al. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. Diabetes Care. 2000;23 : 1130-6

[14] . Fritsche A, Schweizer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedom insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized controlled trial. Ann Intern Med.2003;138:952-9

[15] . Rosenstock J, Schwartz is; CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin filtr'aapy in type 2 diabetes: 28 week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care.2001;24:631-6

[16] .Christopher JD, Greg LP, Gillman MK, Kate M. Insulin glargine: An updated review of its use in the management of diabetes mellitus. Drugs. 2003;63: 1743-78.

[17] . Riddle MC, Rosenstock J. Treatment to target study: Insulin glargine vs NPH insulin added therapy of type 2 diabetes. Diabetes. 2005;51(Suppl2)