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RESEARCH ARTICLE

CLINICAL STUDY OF EARLY INSULIN THERAPY COMPARED TO ORAL HYPOGLYCEMIC AGENTS IN NEWLY DETECTED TYPE 2 DIABETES MELLITUS- A HOSPITAL BASED STUDY

Dr. Usha Rani Pegu¹, Dr. Uttam Kumar Nath², Dr. Diganta Das³ and Dr. Kalpana Chetia¹

1. Associate Professor, Department of Medicine, Jorhat Medical College & Hospital (JMCH), Jorhat-1, Assam.
2. Assistant Professor, Department of Medicine, Jorhat Medical College & Hospital, (JMCH), Jorhat-1, Assam.
3. Assistant Professor, Department of Medicine, Assam Medical College & Hospital (AMCH), Dibrugarh-2, Assam.

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Abstract

Background: As the time progresses, type 2 diabetes usually worsens, oral medications become less effective, and more than a third of people must add insulin injections to their treatment regimen. Primary aim of this study was to assess the efficacy of early insulin therapy in newly detected type 2 diabetes mellitus as compared to oral hypoglycemic agents as a part of the conventional treatment regime.

Materials and Methods: Newly diagnosed type 2 DM or/and diagnosed within the preceding six months, excluding pregnant women and patients with hepatic disorders, renal failure, acute infection, trauma, burns, acute myocardial infarction and malignancies were enrolled in the study.

Results and Observations: 80 patients were selected randomly in two groups treated with OHA (A) and insulin (B). The decrease in FBS, PPBS and HbA1c was not significant ($p > 0.05$) in both the groups with a significant weight gain in group B ($p < 0.05$) after six months of therapy. Follow up loss were 25% in group A as compared to 75% cases in group B.

Conclusion: Improvements in the glycemic status in patients with newly detected type 2 diabetes mellitus treated with OHA and insulin is almost identical. Further studies with large number of patients with prolong duration are needed to arrive at a more clear cut conclusion regarding glycemic efficacy of early initiation of insulin specially in newly diagnosed type 2 diabetes mellitus.

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Introduction:-

Diabetes Mellitus is one of the most common endocrine and metabolic disorders. Diabetes mellitus is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in Insulin secretion, insulin action or both. It is an important health problem that is widely prevalent all over the world and the prevalence has risen dramatically over the past two decades. The prevalence of DM in India ranges from 5–17%, with higher levels found in the southern part of the country and in urban areas^{1,2}. WHO has projected that global prevalence of type 2 DM will more than double from 135 million in 1995 to 300 million by 2025³. The greatest increase will be contributed by the developing nations and India has already been declared as the country

Corresponding Author:- Dr. Uttam Kumar Nath

Address:- Assistant Professor, Department of Medicine, Jorhat Medical College & Hospital, (JMCH), Jorhat-1, Assam.

with the largest number of diabetes in the world. The major chunk of diabetes in India is type 2 diabetes (96% of diabetes in India is type 2 as compared to above 85% worldwide)⁴.

As the type 2 diabetes progresses, the ability of the pancreas to produce insulin may become impaired, and the body does not have enough insulin to move glucose into cells. The oral medications become less effective, and more than a third of people must add insulin injections to their treatment regimen. New research is now challenging this treatment approach, suggesting that adding insulin earlier can greatly improve blood glucose control. (Diabetes Special Report, Johns Hopkins Health Alerts 2005).

In this background it has become necessary to study the efficacy of insulin as an early therapeutic measure in newly detected type 2 diabetes mellitus of this region where no such study has been conducted before. Therefore this study was undertaken with following aims and objectives-

Aims and Objectives:-

1. To study the efficacy of early insulin therapy in newly detected type 2 DM in relation to immediate glycemic control and glycemic control at the end of six months.
2. To study the compliance among the patients treated with oral hypoglycemic agents and Insulin.
3. To study the adverse effects if any of the two modalities of treatment.

Materials and Methods:-

The study was conducted for a duration of one year on newly detected type 2 diabetes mellitus patients diagnosed according to ADA criteria, attending diabetic clinic, out-patient and in-patient department of different medicine units of a tertiary care teaching hospital in North East India after clearance of institutional ethics committee. Patients were selected randomly and informed consent was obtained from all the subjects.

Inclusion criteria:

1. The study included all newly diagnosed type 2 DM patients and patients diagnosed within the preceding six months attending the diabetic clinic and different medicine units.
2. The patient above 30 years of age irrespective of sex.

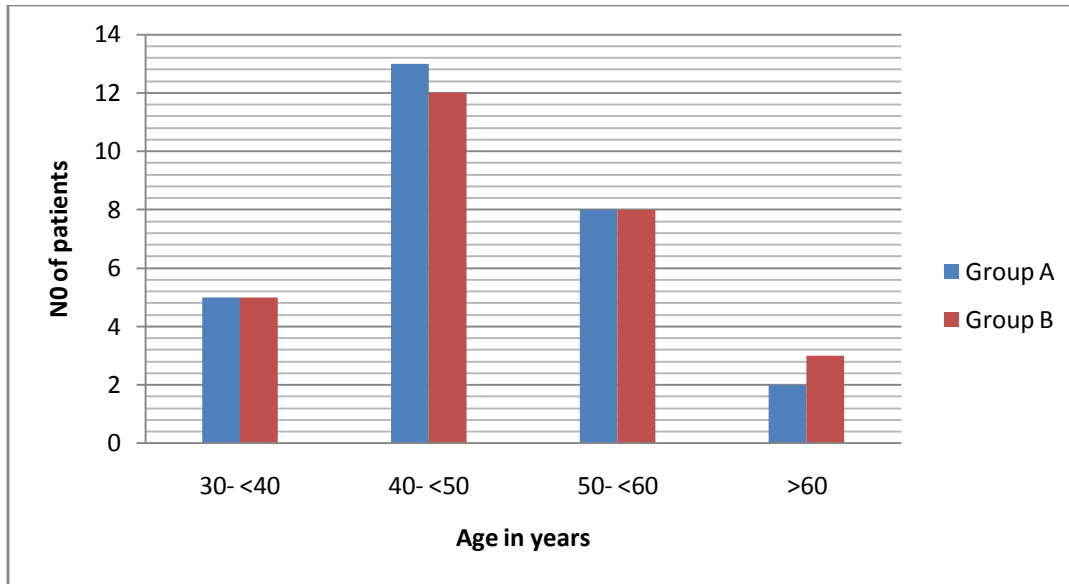
Exclusion criteria:

1. The patients below 30 years of age.
2. Pregnant women, patients with hepatic disorders, renal failure, acute infection, trauma, burns, acute myocardial infarction and malignancies.
3. During follow up if any patient develops medical or surgical emergencies requiring intervention were excluded from the study.

The selected patients were evaluated on the basis of detailed history and clinical examination and investigations with special attention to the glycemic status. Patients were assigned randomly into two groups (A&B) with equal number of patients in each group. Group A was treated with oral hypoglycemic agents. (Both single drug and combination therapy according to the guidelines). Group B was put on insulin, a combination of short acting and intermediate acting insulin. Dose administration frequency, dose adjustment and administration of other drugs were done according to the ADA guidelines⁵. Each case was followed up for 6 months after starting treatment with FBS, PPBS during weekly visit and HbA1c was monitored at the time of diagnosis and after 6 months of follow up. HbA1c was estimated by using cation exchange HPLC system D in the same laboratory. All the patients were also monitored for the adverse effects like hypoglycemia, infection, weight gain, drug overdose, angina, cardiac failure etc. The paired t test was performed and standard deviation and p values of both the groups were calculated. One way analysis of variance (ANOVA) was used to know the difference in the two groups.

Results and Observations:-

A total of 80 patients were selected randomly in two groups. Group A was treated with oral hypoglycemic agents and Group B was put on insulin. Out of the 80 patients 56 were followed up till the completion of six months. The majority of the patients were from the 40 to <50 years age group. The mean age at diagnosis was 46.40 years for all type 2 DM patients.



At diagnosis the mean age was 45.34 years for group A and 46.68 years for group B. There is no significant difference in the mean age in the two groups ($p > 0.05$) Male patients outnumbered female patients in both the groups. Study group A consist of 64.28 % male and 35.71 % female patients whereas group B consist of 60.71 % male and 39.28 % female patients without any significant difference in the mean age in the two groups ($p > 0.05$).

At the time of diagnosis 72.23% male and 70.00% female patients in group A and 83.33% male and 45.45% female patients in group B had FBS ≥ 200 mg%. The mean FBS were 211.89 mg% in group A (male 214.17 mg% and female 207.8 mg %) and 223.75 mg% in group B (male 229.24 mg% and female 215.27 mg %). In group A ,61.11% male and 70.00% female patients and in group B, 88.23% male and 63.63% female had PPBS ≥ 300 mg% at the time of diagnosis. The mean PPBS were 328.79 mg% in group A (male 325.56 mg % female 334.60 mg %) and 336.50 mg% in group B (male 345.41 mg% and female 322.73 mg%).

The mean baseline HbA1c were 11.55% in group A (male 11.62% and female 11.44%) and 11.38 % in group B (male 11.28% and female 11.53%). The mean HbA1c after six month of therapy were 10.76% in group A (male 10.74% and female 10.77%) and 10.64% in group B (male 10.65% and female 10.63%).

Statistical analysis: (Table: 1)

Group	Variable	0-Months(0M)mean \pm SD	1Month(1M) mean \pm SD	P value
Group A	FBS	211.89 \pm 38.43	162.32 \pm 46.61	P<0.001
	PPBS	328.79 \pm 51.74	238.39 \pm 63.69	P<0.001
	Hb1Ac	11.55 \pm 1.46	10.76 \pm 1.49(6M)	p>0.05
Group B	FBS	223.75 \pm 39.23	160.323 \pm 6.73	p<0.001
	PPBS	336.50 \pm 43.59	209.26 \pm 65.12	p<0.001
	Hb1Ac	11.38 \pm 1.38	10.64 \pm 145(6M)	p>0.05

Table 2:

Comparison	Mean difference	P value
FBS-0M Gr.A Vs FBS-0M Gr.B	3.751	p > 0.05
PPBS-0M Gr. A Vs PPBS-0M Gr.B	7.714	p > 0.05
HbA1c-0M Gr. A Vs HbA1c-0M Gr.B	-0.0714	p > 0.05
FBS-1M Gr.A Vs FBS-1M Gr.B	33.464	p > 0.05
PPBS-1M Gr. A Vs PPBS-1M Gr.B	29.036	p > 0.05
HbA1c-6M GA Vs HbA1c-6M Gr.B	0.1036	p > 0.05

There was no significant difference in the base line FBS, PPBS and HbA1c values in the two groups. However after one month there were significant ($p < 0.001$) decrease in mean FBS and PPBS in both the groups. Regarding HbA1c, though there was fall in mean value after six months, statistically it was not significant ($p > 0.05$). (Table: 1&2). On comparing the two groups, the decrease in FBS and PPBS after one month and HbA1c after six months were also not significant ($p > 0.05$) (Table: 2)

Table: 3-Adverse effects in the two groups:

Adverse effects	Group A	%	Group B	%	P value
Hypoglycemia	2	7.14	3	10.71	P>0.05
Infections	9	32.14	5	17.85	P>0.05
Weight gain	5	19.28	20	71.42	P>0.05
Others	1	3.57	0	0	P>0.05

At the time of diagnosis the mean body weight in group A was 64.57 ± 9.28 kg and in group B was 60.85 ± 8.84 kg with a p value 0.1458 ($p > 0.05$). The mean weight gain after six months of therapy in group A was -1.05 and in group B was 2.3 ± 0.5 with a p value of 0.034 ($p < 0.05$). So, there was significant weight gain in group B ($p < 0.05$) as compared to group A. Infection was more in group A (32.14%) in comparison to group B (17.85%). Hypoglycemia in group A was 7.14% and in group B was 10.71%. One patient in group A presented with symptoms of CCF in the study period.

Table: 4:- Compliance in the two groups.

Groups	Follow up Loss	Missed <10% doses	Missed 10-20% doses	Missed >20% doses
Group A	6 (25.00%)	8(28.57%)	5(17.86%)	0(00.00%)
Group B	18 (75.00%)	14(50.00%)	9(32.14%)	7(25.00%)

The total number of follow up loss was 24, out of which 6 patients (25.00%) were from group A and 18 patients (75.00%) were from group B. During follow up 17.86% patients in group A skipped 10% or more OHA doses and 57.14% patients in group B skipped 10% or more insulin doses. ($p > 0.05$).

Discussion:-

The primary aim of the study was to assess the efficacy of early insulin therapy in newly detected type 2 diabetes mellitus versus oral hypoglycemic agents as a part of the conventional treatment regime and to find out the compliance and adverse effects in the two groups.

Age distribution:

In the present study maximum numbers of patients (38.88%) were from the 40 to 50 years age group. The mean age at diagnosis was 46.40 years for all type 2 DM patients, (46.62 years for male and 46.06 years for female). The National Rural Diabetes Survey (1989-1991) found the mean age of subjects with diabetes to be 52.3 years.^{6, 7} Tripathy and Kar found that onset of diabetic cases were above 50 years.⁸ V. Mohan et al found mean age at diagnosis to be around 45 years.⁹ King H et al found that the peak age at diagnosis was 40-45 years in developing countries compared to >60 years in developed countries^{10,11}.

The overall male: female ratio in the present study was found to be 1.7:1. The ICMR Study (1972-1975) found a male: female ratio of 1:0.8. Marianne Zeller et al¹² reported a male to female ratio of 1:0.7. The male preponderance may be due primarily to increase reporting of male cases and reluctance to attend clinics or hospital by female patients.

FBS:

In the present study, at the time of diagnosis 72.23% male and 70.00% female patients in group A and 83.33% male and 45.45% female patients in group B had $FBS \geq 200$ mg%. The mean FBS were 211.89 mg% in group A and 223.75 mg% in group B. After one month of therapy the mean FBS were 160.32mg% in group A (male 167.94mg% and female 152.70 mg %) and 139.81 mg% in group B (male 130.53 mg % and female 149.62mg %).

PPBS:

At the time of diagnosis 61.11% male and 70.00% female patients in group A and 88.23% male and 63.63% female patients in group B had PPBS \geq 300mg%. The mean PPBS in group A was 328.79 mg% (male 325.56 mg% and female 334.60 mg %) and in group B was 336.50 mg% (male 345.41 mg% and female 322.73 mg %). After one month of therapy the mean PPBS were 238.39 mg% in group A (male 240.17 mg% and female 236.60 mg %) and 209.26 mg% in group B (male 212.06 mg% and female 206.51 mg %).

HbA1c:

The mean baseline HbA1c in group A was 11.55% (male 11.62% and female 11.44%) and in group B was 11.38% (male 11.28% and female 11.53%) After six month of therapy, the mean HbA1c in group A was 10.76% (male 10.77% and female 10.77%) and in group B was 10.64% (male 10.65% and female 10.63%). The mean decrease in HbA1c in group A was 0.79% and in group B was 0.74% after six months of therapy.

The decrease in mean FBS and PPBS in both the groups after one month of therapy were significant ($p < 0.0001$), but though there was fall in mean HbA1c value after six months, statistically it was not significant ($p > 0.05$). In Rury R et al¹³ study about the efficacy of complex insulin regimens in type 2 diabetes mellitus found that the decrease in mean FBS was 50 ± 47 and decrease in mean PPBS was 61 ± 58 . In the present study the glycemic status achieved after one month of follow up in both the groups in terms of decrease mean FBS and PPBS were comparable with the above study.

In a 48 weeks study carried out by Meneghini et al on 551 patients found that mean decrease in HbA1c was 2.6% and 2.3% in insulin and OHA groups respectively¹⁴. Another 24 weeks multicentre, open level, parallel study carried out by Rosenstock et al found that the HbA1c improvement from base line in both insulin and OHA groups were similar (mean decrease in HbA1c 1.7% and 1.5% in insulin and OHA groups respectively).¹⁵ In our study the probable reason for not able to find a significant difference in early glycemic status among the two groups is short duration of follow up and small number of patient.

Adverse event:

At the time of diagnosis the mean body weight in group A was 64.57 ± 9.28 kg and in group B was 60.85 ± 8.84 kg with a p value 0.1458 ($p > 0.05$). The mean weight gain after six months of therapy in group A was -1.05 ± 0.3 and in group B was 2.3 ± 0.5 with a p value of 0.034 ($p < 0.05$). Infection was more in group A (32.14%) than in group B (17.85%). Hypoglycemia was seen in 7.14% cases in group A and in 10.00% cases in group B. Meneghini et al study also found that hypoglycemic events were slightly more in the insulin group¹⁴.

Compliance:

In the present study, out of the total 24 follow up loss 6 patients were (25.00%) from group A and 18 patients were (75.00%) from group B. During follow up 17.86% patients in group A skipped 10% or more OHA doses and 57.14% patients in group B skipped 10% or more insulin doses ($p < 0.05$). Rury R et al¹³ found mean increase in weight 5.7 ± 0.5 kg in biphasic insulin group after 3 years of follow up.

Summary:

The majority of the patients (44.46%) were from the 40 to 50 years age group. The mean age at diagnosis was 46.40 years for all Type 2 DM patients with a male: female ratio was 1.67:1.

The base line FBS, PPBS and HbA1c were similar in both the groups without any significant difference ($p > 0.05$). Though there was significant ($p < 0.001$) the decrease in mean FBS and PPBS in both the groups after one month of therapy the fall in mean HbA1c value after six months, was not significant ($p > 0.05$). On comparing the two groups, the decrease in FBS and PPBS after one month and HbA1c after six months was also not significant ($p > 0.05$).

There was significant weight gain in group B ($p < 0.05$) who were on insulin. Hypoglycemia occurs more commonly in this group (7.14% cases in group A and in 10.00% cases in group B). Infection was more in group A who were on oral hypoglycaemic agent (32.14% Vs 17.85%).

Compliance to the therapy was better in those patients who were on oral hypoglycaemic agent. Follow up losses were much more in insulin treated group as compared to OHA treated group (75% Vs 25 %). In group B who were receiving insulin 25.00% patient skipped 20% or more doses of insulin during follow up.

Conclusion:-

Improvements in the glycemic status in patients with type 2 diabetes mellitus treated with oral hypoglycemic agents and insulin was almost identical ($p>0.05$). Patients on insulin showed high incidence of weight gain ($P<0.05$). The compliance was better with oral hypoglycemic agents. Overall, in the present setting insulin is not better than oral hypoglycemic agents in newly diagnosed type 2 diabetes mellitus patients. Further studies with large number of patients with prolong duration are needed to arrive at a more clear cut conclusion regarding glycemic efficacy of early initiation of insulin specially in newly diagnosed type 2 diabetes mellitus.

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