ORIGINAL ARTICLE

Comparative Study of Efficacy and Safety between Human Soluble Insulin and Biphasic Isophane Insulin in Type II Diabetic Mellitus

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Abstract

Among different insulin preparations available for the management of type II diabetes mellitus (DM), human soluble regular insulin (Human Actrapid) and human biphasic isophane insulin (Human Mixtard) are commonly prescribed agents. We compared the efficacy and safety of both the insulin for glycemic control in type II DM. Effects on lipid profile is also assessed. Fasting blood sugar was found to improve in both groups but the percentage change in Mixtard group (14.5%) was more than Actrapid group (6.26%). Postprandial blood sugar level also was better controlled in Mixtard group (14.4%) than Actrapid group (5.19%). Both the drugs were well tolerated without any alarming side effects. In Mixtard group, total cholesterol, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were controlled better whereas high density lipoprotein (HDL) and triglyceride were found to be improved more in Actrapid group. Hence it can be concluded that blood sugar control is better with Mixtard group.

Keywords: *Actrapid, Diabetes Mellitus, Human Biphasic Isophane Insulin, Human Soluble Regular Insulin, Mixtard*

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Introduction

Diabetes Mellitus currently affects 246 million people worldwide. It is projected to affect 366 million people in the world by 2030. The International Diabetes Federation recently published findings revealing that in 2007, the country with the largest numbers of people with diabetes is India (40.9 million), followed by China (39.8 million) [1,2].

Type 2 diabetes mellitus is characterized by progressive β-cell destruction and insulin resistance. As β -cell function declines, many patients with type 2 diabetes require insulin therapy on long run. Clinical studies show that tight control of blood glucose levels prevents the development of the microvascular and macrovascular complications caused by diabetes [3]. The burden of diabetes on the health care system mandates efforts to more optimally treat those with the disease and to prevent its development in those at risk. Insulin is the most potent drug currently available to achieve tight glycaemic control.

Among different insulin preparations, human soluble regular insulin (Human Actrapid) and human biphasic isophane insulin (Human Mixtard) are commonly prescribed drugs for the management of type 2 diabetes mellitus. In the present study we compared the efficacy and safety of both the insulin for glycemic control in type II DM. Effects on lipid profile is also assessed.

Materials & Methods

The present study is a randomized, open labeled, comparative clinical study between human soluble and biphasic isophane insulin in type II diabetis mellitus (DM) patients. It is a single centric study conducted on out patients department (OPD) basis at the department of general medicine, Prathima Institute of Medical Sciences, Nagunur, Karimnagar, Telangana, India. Sample size of 60 was calculated for the

study. Procedures followed in this study were in accordance with the ethical standard laid down by ICMR's Ethical guidelines for biomedical research on human subjects (2006).

Included cases were of type 2 diabetes mellitus not responding to oral hypoglycemic agents, and those who were free from other significant morbidity including infection, inflammation, or any neoplasm. All the patients aged 30 years or above were part of the study. Patients on statins, angiotensin converting enzyme inhibitors and angiotensin receptor blockers were excluded from the study. Pregnant and nursing females and patients hypersensitive to insulin were also excluded from the study. Written informed consent was obtained before commencing the study from the patients.

All the patients were divided randomly in two groups of 30 each (Actrapid and Mixtard). At the first visit, after clinical evaluation and laboratory investigations, in Actrapid group human soluble insulin and in other group (Mixtard group) human biphasic isophane insulin was prescribed for a period of 1 month. No medications that could interfere with the clinical evaluations were allowed during the trial.

In the follow-up (after completion of one month) 6 patients were lost in Actrapid group and 5 patients in Mixtard group. So finally, in Actrapid group 24 patients and in Mixtard group 25 patients completed the trial. At 1 month follow-up, detailed resume of clinical state were made including the hospital investigations and therapy. Physical examination including, height, weight, BMI, abdominal circumference were assessed. Laboratory investigations conducted were, fasting and post-prandial blood sugar, glycosylated Hemoglobin (HbA_1c %), and lipid profile. Fasting and post-prandial blood sugar was estimated by Glucose Oxidase-Peroxidase (GOD-POD) method while Glycosylated Hemoglobin (HbA_1c %) was estimated using Chromatographic-Spectophotometric ion exchange method. Methods for lipid profile estimation were;

- Cholesterol: "CHOD-PAP": Enzymatic Photometric Test [4]
- Triglycerides: Colorimetric enzymatic test using glycerol-3-phosphate oxidase (GPO) [5]
- HDL Cholesterol: Phopho Tungstatic acid method [6].

Safety and tolerability were assessed on the basis of the adverse events reported, or comparing the baseline symptoms with post-drug symptoms, or changes in vital signs, and physical examination findings recorded before and after the end of treatment.

Results

The baseline demographic data and clinical characteristics of all 60 patients participated in this study have been compared in the table- 1 and the p values suggest that there is no statistically significant difference in between the study groups in the parameters studied in the first visit. This proves the homogeneity of our study subjects in two groups.

Blood Sugar

Fasting blood sugar (FBS) was found to improve in both groups but the percentage change in Mixtard group (14.5%) was more than Actrapid group (6.26%). Similarly postprandial blood sugar (PPBS) level also was better controlled in Mixtard group (14.4%) than Actrapid group (5.19%). The finding shows statistical significance in favor of Mixtard group ($p = 0.03$) table- 2.

Glycosylated Hemoglobin (HbA_{1c} %)

Glycosylated hemoglobin which is a marker of long term glycemic control, was decreased by 5.26% ($p=0.01$) in Actrapid group in comparison to 6.33% ($p=0.0005$) in Mixtard group and this difference was found not to be statistically significant ($p=0.45$) by t-test (Table-3.

Lipid Profile

In both the groups, the changes in lipid profile after one month of medication was found to be favorable. In Actrapid group, there was 4.49% ($p=0.01$) decrease in total cholesterol, 7.04% decrease ($p=0.006$) in LDL, 7.12% ($p=0.001$) increase in HDL, 2.83% ($p=0.08$) decrease in VLDL and 9.43% ($p=0.001$) decrease in triglyceride level. On the other hand, in Mixtard group, there was significant changes in total cholesterol (7.01%; $p=0.0001$), LDL (10.5%; $p=0.0001$), HDL (4.05%; $P=0.02$), VLDL (4.53%; $p=0.02$), triglyceride (8.48%; $p=0.02$). When the changes of both the groups were compared by t-test, no significant change was found in either parameter (Table- 4).

Table- 1: Baseline comparison between the groups

Characteristics	Actrapid Group	Mixtard Group	p value
Age (years)	51.03±9.3	53.97±8.7	0.21
Duration of diabetes (years)	4.6±4.7	5.4±4.6	0.49
BMI (kg/m^2)	22.5±3.9	24.88±5.6	0.06
Waist circumference (inch.)	33.7±4.3	33.4±5.4	0.78
Systolic Blood Pressure (mm Hg)	135.7±13.2	137.0±11.1	0.29
Diastolic Blood Pressure (mm Hg)	89.2±9.2	92.2±6.2	0.14
Fasting Blood Sugar (mg/dl)	202.1±43.7	219.7±56.2	0.18
Post-prandial Blood Sugar (mg/dl)	277.3±57.0	283.0±68.7	0.72
HbA_{1c} %	8.16±2.04	7.78±1.37	0.41
Total Cholesterol (mg/dl)	209.4±25.5	216.3±31.7	0.35
LDL Cholesterol (mg/dl)	138.9±23.7	146.4±31.4	0.29
HDL Cholesterol (mg/dl)	38.2±4.4	36.7±2.7	0.11
VLDL Cholesterol (mg/dl)	32.3±2.9	33.3±2.9	0.22
Triglyceride (mg/dl)	198.1±53.9	175.4±62.8	0.14

Data are in Mean ± SD, LDL- Low density lipoprotein, VLDL- Very low density lipoprotein, HDL- High density lipoprotein

Table- 2: **Blood Sugar assessment**

Sugar Level (mg/dl)	Actrapid Group (Mean±SD)				Mixtard Group (Mean±SD)				Group Difference
	1st Visit	2nd Visit	% Change	p value	1st Visit	2nd Visit	% Change	p value	
FBS	211.0 ±44.1	197.8 ±26.6	6.26	0.01*	223.7 ±55.6	191.2 ±19.7	14.5	0.0007*	0.15
PPBS	269.3 ±56.8	255.3 ±47.4	5.19	0.03*	289.7 ±67.5	248.1 ±44.2	14.4	0.0001*	0.03*

Table- 3: Glycosylated Hemoglobin (HbA_{1c} %)

HbA_{1c} %	Actrapid Group (Mean±SD)				Mixtard Group (Mean±SD)				Groups Difference
	1st Visit	2nd Visit	% Change	p value	1st Visit	2nd Visit	% Change	p value	
	7.99 ±2.25	7.57 ±1.75	5.26	0.01*	7.90 ±1.33	7.40 ±1.16	6.33	0.0005*	0.45

Table- 4: Lipid profile assessment

Lipids Level (mg/dl)	Actrapid Group (Mean±SD)				Mixtard Group (Mean±SD)				Group Difference
	1st Visit	2nd Visit	% Change	p value	1st Visit	2nd Visit	% Change	p value	
Total Cholesterol	211.7 ±27.6	202.2 ±17.9	4.49	0.01*	211.0 ±26.3	196.2 ±20.6	7.01	0.0001*	0.25
LDL	142.0 ±25.2	132.0 ±16.9	7.04	0.006*	140.9 ±25.3	126.1 ±20.3	10.5	0.0001*	0.27
HDL	37.9 ±4.0	39.2 ±2.6	7.12	0.001*	37.0 ±2.8	38.5 ±2.0	4.05	0.02*	0.93
VLDL	31.8 ±2.6	30.9 ±2.4	2.83	0.08	33.1 ±2.8	31.6 ±1.4	4.53	0.02*	0.58
Triglyceride	206.8 ±57.0	187.3 ±36.8	9.43	0.001*	178.1 ±66.2	163.0 ±63.5	8.48	0.02*	0.82

Safety Assessment

Both the drugs were well tolerated without any alarming side effects. In Actrapid group 7 patients complained hypoglycemic episodes and one patient suffered from lipoatrophy. 2 patients who were on Mixtard insulin complained of hypoglycemia and another 2 had lipohypertrophy at injection sites. Though episodes of hypoglycemia was found to be more in Actrapid group, Fisher's exact test found to be non-significant (p=0.07).

Discussion

In both Actrapid and Mixtard group, blood pressure was well controlled. In Actrapid group change in SBP was not statistically significant but DBP was lowered significantly. In Mixtard group both SBP and DBP were decreased

significantly. In our study insulin therapy has been found to be associated with decrease in the blood pressure supporting the earlier study by Tim Heise et al. in 1998 [7]. The possible explanation behind this blood pressure control might be insulin induced vasodilatation [7].

The changes in fasting and post-prandial blood sugar are statistically significant in both the study groups but the comparative study by t-test reveals that the control of postprandial blood sugar was better in Mixtard group in comparison to Actrapid. To assess the long-term glycemic control, Glycosylated hemoglobin (HbA_{1c} %) has been estimated. It was decreased by 5.26% (p=0.01) in Actrapid group in comparison to 6.33% (p=0.0005) in Mixtard group and this difference was found not to be statistically significant (p=0.45) by t-test. In a study conducted by SuCC et al with different combination of Mixtard insulin showed more reduction of PPBS levels with Mixtard 50 HM [8]. The better glycemic control with biphasic insulin is attributed to its pharmacokinetic properties like quick onset and longer duration of action.

After one month of insulin treatment there was statistically significant improvement in all parameters of lipid profile in Mixtard and Actrapid groups except VLDL in Actrpid group. In Actrapid group percentage change in total cholesterol, LDL, VLDL was less than Mixtard group. HDL and triglycerides were found to be better controlled with Actrapid. When the changes in Mixtard group was compared with Actrapid group, no statistical significance was found but it was evident that in Mixtard group Cholesterol and VLDL were better controlled than Actrapid group. Our observations on the effect of insulin on lipid profile parameter supports the earlier studies by Das et al. 1993 [9].

In the present study we found both human soluble regular insulin and biphasic isophane insulin are well tolerated drugs. There were no serious or new side effects complained by the patients. Discontinuation of the drug was not required for those reported side effects in either group.

Conclusion

It is concluded that Actrapid and Mixtard decreases HbA1c but both the drugs do not have significant superiority over each other. Mixtard has better control over postprandial blood sugar. Mixtard has better control over Total Cholesterol, LDL cholesterol and VLDL while HDL control is better with Actrapid. Both the drugs are equal in term of safety. Human biphasic insulin can be a better choice in type 2 diabetes mellitus not responding to oral hypoglycemic drugs because of higher percentage of improvements in most of the parameters studied.

Conflict of Interest: *None declared*
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