EFFECT OF DIFFERING SOLUBLE INSULIN RATIO ON METABOLIC CONTROL - A PROSPECTIVE, MULTI-CENTRIC, OBSERVATIONAL STUDY ON HUMAN MIXTARD® 30 AND HUMAN MIXTARD® 50 IN POORLY CONTROLLED, INSULIN REQUIRING DIABETICS*

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ABSTRACT

Several studies have indicated that the degree and duration of postprandial hyperglycemia [PPHG] correlates well with the incidence, severity, and rate of progression of diabetic complications. This evaluation of the comparative efficacy of two different insulin formulations, Human Mixtard® 30 and Human Mixtard® 50, was done to see whether providing more soluble insulin along with NPH insulin in premixed, biphasic, insulin formulations would help improve control of postprandial hyperglycemia and overall glycemic control as measured by glycated haemoglobin estimation (GHb). A total of 279 investigators (general practitioner, physician, diabetologist or endocrinologist) participated in the study and a total number of 5009 patients were recruited and completed the study. A specially designed proforma that included data on medical history, anthropometry, physical examination, meal patterns, drug therapy, presence/absence of complications, adverse effects experienced and laboratory investigations was filled in at baseline and after three months of therapy with the prescribed insulin formulation. In this clinical study, an improvement in all glycemic parameters was seen in both groups between the two visits, three months apart. The mean reduction in 2h PPBG was higher in the Human Mixtard® 50 group as compared with the Mixtard® 30 group [109 versus 95.6 mg/dl (p=0.0001)], whereas the reduction in FPG was similar [65.1 vs. 64.4 mg/dl]. The mean GHb was lower in the Human Mixtard® 50 group [1.91 % vs. 1.82 %]. The mean incidence of hypoglycemic events reduced from 0.83 events per patient per month to 0.63 events per patient per month at the end of the study period. This study demonstrates that poorly controlled diabetes can change to good glycemic control in a relatively short time when insulin therapy is initiated. Both formulations are safe and effective, but Human Mixtard® 50 helps achieve better control of postprandial hyperglycemia, at no additional risk.

KEY WORDS: Poor glycemic control; Postprandial hyperglycemia; Insulin requiring patients; Hypoglycemia; Human premixed insulin; Human Mixtard 30/70; Human Mixtard –50.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Diabetes mellitus affects populations across the globe. The number of adults with diabetes in the world is predicted to rise from 135 million in 1995 to 300 million in 2025.The major part of this numerical increase will occur in developing countries with a 170% increase from 84 million to 228 million.

India has the largest population of diabetic patients in the world (1) and there are an estimated 25 million persons with diabetes in India (2). The rate has steadily increased in urban population from 2% in the early 1970's to about 11.6%in 1996 (3) and is likely to be even higher according to a recently completed National Diabetes Epidemiological study (4).

Untreated or improperly managed diabetes leads to complications, adding to the economic burden of diabetes. Studies like DCCT (5), UKPD study (6) and Kumamoto (7) have all shown that tight glycemic control can prevent, retard or arrest development of complications both in type 1 and type 2 diabetes and thereby decrease the cost of diabetes related complications.

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In recent years, the post prandial state has received much attention. This is due to the fact that several epidemiological studies have indicated that post prandial hyperglycemia (PPHG) correlates with the occurrence of diabetic complications (8), notably retinopathy and nephropathy. Moreover PPHG even in the absence of marked fasting hyperglycemia is a recognized risk factor for coronary artery disease (CAD) and normalizing PPHG in pregnant women with diabetes mellitus is associated with better pregnancy outcomes. Therefore, the need to control PPHG in addition to fasting hyperglycemia and thereby achieve a 24-hour good glycemic control is the topmost priority on the mind of the practicing physician and is much sought after need of the diabetic patient.

Early in the natural history of type 2 diabetes where PPHG is the major problem, the meglitinide group of drugs such as Repaglinide (NovoNorm), or the glucosidase inhibitors such as Acarbose are emerging as the mainstay in therapy. However, as the disease progresses and beta cell function deteriorates many patients require insulin replacement therapy.

Patients with diabetes mellitus who require insulin are often treated with variable ratios of short and intermediate acting insulin in the belief that such regimens will optimize glycemic control. It is reasoned that because of differing eating patterns and variable rates of absorption of foods, the mix of injected insulin must be tailored to meet the individuals needs. However, much of the variability in blood glucose levels may be due to erratic insulin absorption, and probably cannot be improved by "fine tuning" of the proportions of short acting and intermediate acting insulin (9,10). Such regimens while not improving control significantly are difficult to follow and supplement. It is possible that premixed preparations could help overcome the inconvenience of mixing insulin products without compromising on glycemic control. Moreover, it has been shown that self-mixing errors can lead to inaccurate dosing and poor glycemic control (11). Consistent with this is the demonstration that more accurate dosing is achieved by using premixed insulin.

While the use of a broad range of insulin ratios have been challenged on the basis of limited therapeutic need and the problems associated with self-mixing, nonetheless, with an increased focus on post-prandial glucose level, a ratio with a higher proportion of soluble insulin may offer some advantages. Consequently, the present study was envisaged to collect data on the comparative efficacy of Human Monocomponent Biphasic [30:70] Isophane Insulin [Human Mixtard®] and Human Monocomponent Biphasic [50:50] Isophane Insulin [Human Mixtard®50] in Indian diabetic patients.The objective of the study was to evaluate the comparative efficacy of Human Mixtard® and Human Mixtard® 50 in insulin requiring Indian diabetic patients.

MATERIALS AND METHODS:

Across the country, 279 investigators including endocrinologists, diabetologists, physicians and general practitioners participated in this study. A total of 5009 insulin requiring, diabetic patients were recruited for the study.

The study included at least two mandatory visits, one at baseline and the other after three months of treatment, during which the subjects received either Human Mixtard® or Human Mixtard® 50. The decision to assign treatment to either preparation was based on clinical decision made by the treating doctor. While assigning the treatment, the doctor stated the reason for choosing the particular therapy, which was either based on meal pattern or the blood glucose levels. A standard Case Record Form (CRF) was used to collect data from all centers. The CRF was designed to collect exhaustive baseline information on patient demographics including sex, age, height, weight, waist and hip circumference and patient's diabetes history, which included duration of diabetes and its treatment and the type of diabetes mellitus.

The status of microvascular and macrovascular complications were also noted at baseline along with other relevant information on other associated conditions. Changes in insulin dose and treatment modifications were done based on clinical judgment and blood glucose measurements, as is naturally done in day to day practice. No attempt was made to modify the prevailing practice of the participating doctor.

To demonstrate the effect of treatment with either preparation, the status of glycemic control at baseline and after three months treatment was recorded. Investigations included fasting (FBG), post-prandial (PPBG), random blood glucose and GHb estimations. The provision for recording GHb was optional and left to the discretion of the investigators.

Any blood glucose measurements done in between to titrate insulin dose or as a routine were not recorded on the CRF. The number of hypoglycemic attacks and the occurrence of adverse events were used to asses safety. The frequency and severity of hypoglycemic attacks in the three months prior to visit 1 were compared to the frequency and the severity of the hypoglycemic attacks at the end of three months, in both treatment groups.

The CRF was also designed to collect data pertaining to meal pattern of the patients, including the number of meals and the number of snacks per day and the approximate percentage calorie distribution for various meals and snacks. The reason for choosing the type of insulin, the overall subjective impressions of the patients and the investigators about the particular treatment in the given patient, were also recorded.

On completion of the study, case record forms were collected and subjected to a thorough scrutiny and validated. After validation, a total of 5009 CRF's were subjected to data analysis. Many cases had missing data. Data from paper forms were entered into a PC and calculations were done using SPSS version 8.0. The statistical analysis of various parameters was performed on the available data as recorded in the CRFs.

RESULTS

Men constituted 56.7 % of the study subjects. The mean age for males and females was 50.7 ± 13.0 years and 48.7 ± 17.7 years respectively. Type 1 diabetes was reported in 13.3%, type 2 in 83.4%, gestational diabetes in 0.4%, pre-gestational diabetes in 0.9% and other types of diabetes in 2% of patients.

Amongst patients below 30 years of age 71.1% were type 1, while 93.1% patients above 45 years had type 2 diabetes. The mean body mass index (BMI) for males was 24.3±5.6 and for females 25.5 ± 6.4. Almost half (48.7%) of the female patients had a BMI >25; correspondingly only 22.3% of male patients had a BMI >27. The mean WHR for males was 1.03 ± 0.12 with 52% having a WHR > 0.95, correspondingly 93% of female patients had a WHR more than 0.8 with a mean WHR of 0.95 ± 0.13. The mean duration of diabetes was 9.0 ± 6.4 years and the mean duration of diabetes treatment was 7.9 ± 6.2 years. Majority of patients had a diabetes duration exceeding five years.

Table 1: Demographic Characteristics of the Study Population.

Parameters	Total	Human Mixtard	Human Mixtard 50
Age (years)	50.0 ± 13.8	50.2 ± 14.0	49.8 ± 13.3
Duration (years)	8.9 ± 6.4	9.0 ± 6.6	8.8 ± 6.1
Male / Female*	2177/1659	1237/990	940/669
BMI	24.6 ± 4.9	24.6 ± 4.9	24.6 ± 5.0
WHR*	0.95 ± 0.1	0.96 ± 0.1	0.95 ± 0.1
Retinopathy	2725	1568 (36.9 %)	1157 (35.2%)
Renal problems	2608	1508 (28.7 %)	1100 (25.1%)
Neuropathy	2823	1610 (37.5 %)	1213 (37.8%)
Cardiovascular	2623	1508 (26.9 %)	1115 (24.5%)
Cerebrovascular	2421	1391 (6.9 %)	1030 (5.4%)
Peripheral vascular	2521	1450 (11.8 %)	1071 (9.2%)

** Difference between Human Mixtard and Human Mixtard 50, p<0.05.*

Table 2: Glycemic Control with the Treatments

Assessment	GHb%		FBG		PPBG	
	Human Mixtard	Human Mixtard 50	Human Mixtard	Human Mixtard 50	Human Mixtard	Human Mixtard 50
n	667	583	1258	941	1233	950
Visit 1	9.8%	9.8%	191.6	192.5	273.5	286.7
	(2.2)	(2.1)	(63.2)	(63.4)	(84.7)	(82.4)
Visit 2	7.93%	7.88%	127.2	127.4	177.8	177.2
	(1.33)	(1.31)	(36.8)	(35.1)	(45.9)	(43.7)
Difference	1.82%*	1.91%*	64.4*	65.1*	95.6*	109.6*@
	(1.89)	(1.88)	(60.2)	(57.4)	(84.5)	(78.8)

** : Difference between visit 1 and visit 2, p<0.05*
@ : Difference between the two treatments p<0.001.

The demographic characteristics of the study population are as shown in table 1.The two groups were well matched and there was no statistically significant difference between the groups except for a higher WHR in the Mixtard-30 group mainly due to a relatively higher proportion of male patients. Overall, status of complications was available in 4079 patients. Of these 1690 i.e., 41.4% patients were free of complications while the remaining 59.6% patients had either one (25.1%); two (16.2%); or three or more complications (17.2%). Increased duration of diabetes was associated with a higher rate of both microvascular and macrovascular complications. Microvascular complications were present at baseline in 41 % and macrovascular complications in 22 %. Amongst the macrovascular complications cardiovascular disease was noted in 17%,

cerebrovascular in 5% and peripheral vascular in 7% of the patients. Associated hypertension was present in 60.5%. of the 4773 patients in whom data was available.

A significant improvement in all glycemic parameters was seen with both insulin treatments within the study duration of three months. Table 2 demonstrates the glycemic parameters with respect to GHb, FBG and PPBG. The Human Mixtard 50 group demonstrated a better glucose control i.e., significantly greater reduction in PPBG (p=0.0001), as well as a tendency to a greater, although statistically non-significant, reduction in GHb and FBG. The mean daily dose of Human Mixtard® 30 was 31.3 IU at the beginning of the study and 34.3 IU at the end of the three month period, corresponding values for Human Mixtard® 50 were 32.8 IU and 35.7 IU respectively. These values were statistically not different either between the groups or between the start and end of the study. No treatment emergent adverse events were reported during the study period. The mean incidence of hypoglycemic events reduced from 0.83 events/month at baseline to 0.63 events/month at the end of the study period. This was not statistically significant.

The reasons for choosing the two premixed insulin types were not significantly different for either of the parameters - meal pattern (41% and 42%), blood glucose (47% and 47%), others (12% and 11%) respectively for Human Mixtard ® 30 and Human Mixtard® 50. Data for meal patterns were available for 2601 patients. Of these, approximately 35% had two meals per day, and 61.5 % had three meals a day. The PPBG values in the two treatment groups differed significantly in favour of Human Mixtard® 50 who took at least two meals per day. No snacks were taken by 6.4% patients, one snack per day by 17.9%, two snacks by 49.4 %, three snacks by 20.1% and more than three snacks per day by 6.2% patients.

Over 97% of patients and physicians graded the treatments from very good to satisfactory.

DISCUSSION

The prevalence of diabetes in India has reached epidemic proportions. Findings from the recently concluded DESI study indicated the urban prevalence of diabetes to be 13.2%. Moreover, an equally high prevalence of impaired glucose tolerance is noted in the study.

Type 2 diabetes constitutes approximately 90% of all diabetic persons in India (12). In the present study, approximately 84% of all patients studied had type 2 diabetes and the average duration of diabetes was approximately nine years. This is similar to the data reported from the Diabcare Asia Study (12). The age of onset of diabetes in India seems to be in the early forties (13,14). A finding that is consistent with other studies carried out by us. The significance of this finding in the context of the study is that many of the these patients with a relatively earlier onset of diabetes may require insulin therapy for optimal control later in life.

Human Mixtard® and Human Mixtard® 50 are the most widely used premixed insulin. In the present study, significant improvement in all glycemic parameters was seen with the use of both premixed insulin ratios. A significant mean reduction of about 18-19% in GHb, 33-34% in FBG and 35-38% in PPBG was noted, clearly indicating effectiveness of premixed insulin in Indian patients. Also Human Mixtard® 50 produced a significant reduction in PPBG as compared to Human Mixtard® making it the insulin of choice to reduce postprandial blood glucose. Several epidemiological studies have shown that postprandial hyperglycemia alone is associated with an increase in the occurrence of complications, particularly macrovascular complications.

The UKPD study, Kumamoto and other studies have clearly demonstrated the benefits of improving metabolic control in reducing the risks of both micro and macrovascular complications. Despite improved control the frequency of hypoglycemic episodes actually reduced, suggesting that several other factors, besides insulin therapy, are responsible for the occurrence of hypoglycemia including missing or delaying a meal or inconsistent exercise. The use of higher ratio of soluble insulin in Human Mixtard® 50 was not associated with any more risk of hypoglycemia. In fact for patients and physicians who worry about the risk of hypoglycemia, Human Mixtard® 50 is a better option as a greater proportion of insulin is working in conjunction with the meal related rise in glucose. Data on meal pattern indicates that most diabetics take 2-3 meals per day, thus making Human Mixtard® 50 a very good treatment option for most insulin requiring type 2 diabetic patients, particularly for those who eat two large meals. Both ratios were well accepted by patients and physicians alike.

The study provides several important insights and is therefore important for several reasons. It helps profile insulin requiring persons with diabetes in India based on large cross sectional data from across the country. It shows that poorly controlled diabetics can attain good glycemic control in a relatively short period of time when insulin therapy is initiated. It indicates that in relatively poorly controlled patients, moderately aggressive treatment with two differing premixed insulin preparations is not associated with an increased risk of hypoglycaemia. It shows that while both premixed insulin ratios are effective and safe, Human Mixtard® 50 produces a significantly greater fall in 2h PPBG levels than Human Mixtard and maybe a preferred therapy for the management of insulin requiring patients whose major problem is difficult to control post-prandial hyperglycemia.

REFERENCES

1. King H, Aubert RE, Hermann WH, Global Burden of Diabetes, 1995-2025. Diabetes Care 1998; 21(9): 1414-31
2. Kapur A, Shishoo S, Ahuja MMS, Sen V, Mankame K. Diabetes care in India-physician perceptions attitudes and practices (DIPPAP-2 study). Int J Diab Dev Countries 1998; 18(4): 124-30.
3. Ramaiya KL, Kodalli VRR, Alberti KGMM. Epidemiology of diabetes in Asians of the Indian subcontinent. Diabetes Metab Rev 1990; 6: 125-46.
4. DESI study- under publication
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treament of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New Eng. J. Med. 1993; 329 (September 30): 971-86.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.
7. Ohkubo Y, Kishikawa H, Araki E, et al; Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomised prospective 6-year study. Diabetes Research and Clinical Practice, 1995; 28: 103-17.
8. Arshag D.Mooradian and Jerome E.Thurman: Drug therapy of postprandial hyperglycaemia. Drugs 1999; 57(1).
9. Galloway JA, Spradhwi CT, Nelson RS, et al. Factors affecting the absorption, secretion, serum insulin concentrations, and blood glucose responses after injection of regular insulin and various insulin mixtures, Diabetes Care 1981; (4) 366-76.
10. Corcoran J.S., Yudkin JS. A comparison of premixed and patient mixed insulins. Diabetic Medicine 1986; (3) 246-9.
11. Arnoff, Goldeberg R, D et al; Use of a pre mixed Insulin regimen (Novolin 70/30) to replace self-mixed insulin regimens. Clinical Therapeutics.1994; 16(1) 41-8.
12. Diabcare-Asia – Under publication
13. Kapur A, Shishoo S, Ahuja MMS, Sen V, Mankame K. Diabetes care in India-patient's perceptions attitudes and practices (DIPPAP-1 study). Int J Diab Dev Countries 1997;17(1): 5-17
14. Rayappa PH, Raju KNM, Kapur A, Bjork Stephen, Sylvest Camilla, Dilip Kumar KM. Economic Cost of Diabetes Care: The Bangalore Urban District Diabetes Study. Int J Diab Dev Countries 1999;19 (3): 87-96.