USE OF MONOCOMPONENT INSULINS AND THE COURSE OF DIABETIC RETINOPATHY – A FOLLOW-UP STUDY

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INTRODUCTION :

Monocomponent insulins (M.C. insulins) represent a major advance in the treatment of problem cases of diabetes mellitus [1-3]. The specific indications of M.C. insulins include insulin allergy, insulin resistance, lipoatrophy and other problems with conventional insulins. We have earlier demonstrated that M.C. insulins help to reduce the elevated insulin antibody titres [4-6]. To date however there are no studies which have looked at the clinical benefits of the reduction in the elevated antibody titres. It has been suggested that immune complexes are reduced after treatment with these insulins[7] and that there might be some beneficial effects on nephropathy. None of the earlier studies have looked at the course of retinopathy in patients treated with insulins of different purity. In this study the effect of treatment using monocomponent insulin was compared with that of conventional insulin with respect to the course of mild diabetic retinopathy.

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MATERIALS AND METHODS :

Since it is well known that in advanced stages diabetic retinopathy is an irreversible process, subjects with early retinopathy were chosen. Patients had NIDDM type of diabetes but were now in an insulin requiring stage. All patients had duration of diabetes exceeding 10 years and had been treated for atleast two years with conventional insulins prior to the trial. Baseline investigations included fasting and post- prandial plasma glucose (Glucose oxidase, Boehringer Mannheim), HbAl estimations[8] and lipid studies. Insulin antibody[9] and C-peptide[10] estimations were done by radioimmunoassay.

A detailed eye examination was done by an ophthalmologist trained in diabetic retinopathy. This included recording of the visual acuity, measuring the intraocular pressure and biomicroscopic examination of the anterior segment. The pupils were then fully dilated and a detailed retinal examination was done using direct and indirect ophthalmoscopy. The diabetic retinopathy was carefully graded using the Hammersmith Hospital grading system[11]. A detailed clinical assessment was made as detailed below. The method of grading of lesions was to compare the lesions seen on ophthalmoscopy with a set of standard colour photographs showing different grades of severity. Specific lesions of diabetic

retinopathy namely microaneurysms and dot haemorrhages, hard exudates, intraretinal microvascular abnormalities (IRMA), new vessels and retinitis proliferans were looked for. Each quadrant of the eye was separately graded for the presence of these lesions. Each lesion was assigned a score of 1-5 based on the severity. In this manner a quantitative assessment of the retinopathy was possible. Based on the severity, the retinopathy was graded as minimal, mild, moderate or severe. At onset most patients had comparable severity of retinopathy namely minimal or mild retinopathy.

Patients were then randomly allotted to either the M.C. Insulin (Novo, Denmark) or the conventional insulin (Boots, India) group. All patients were put on a combination of short acting and intermediate acting insulins (Actrapid M.C. and Monotard M.C. or Plain and Lente insulins respectively). The dose of insulins were adjusted to the individual needs. Follow-up studies were done at yearly intervals. At each visit the plasma glucose and HbAl estimations were repeated. The patients underwent the eye examinations exactly as on the initial visit. The ophthalmologist was unaware of the treatment the patient was receiving. Increase or decrease in the severity of the lesions by two grades in the microaneurysms and haemorrhages was considered as progression or regression respectively. Statistical analysis was done using paired and unpaired 't' tests and Fischer's exact probability test.

RESULTS :

A total of 50 patients were initially selected in each group. However there were some drop-outs and 43 patients completed the first year follow up in the M.C. insulin group and 28 patients in the conventional insulin treated group. At the end of 3 years these numbers came down further. 17 patients in the M.C. insulin group and 15 patients in the conventional insulin treated group completed 3 years of the study. Since the changes observed at the end of the first year were not appreciable, only the 3 year follow up results are given.

Table 1 shows the clinical details of the study groups. In can be seen that there are no significant differences in the age, age at diagnosis, the duration of diabetes or the C- peptide levels between the two groups.

Table 2 shows the changes in plasma glucose and HbAl after treatment in the two groups. There was no significant difference between the two groups with respect to the initial severity of diabetes or the control of diabetes (HbAl levels). The dose of insulin in the conventional insulin group was higher than in the M.C. Insulin treated group but this was not significant statistically.

Table 3 summarises the results of the changes in the retinopathy status of the patients in the two groups. While 29% showed improvement in the retinopathy status in the M.C. Insulin treated group, 13.3% of the conventional insulin treated group showed improvement. Due to the small study numbers these differences did not reach statistical significance. In the conventional insulin treated group 33.3% of patients showed progression in the retinopathy compared to 29% in the M.C. Insulin treated group. One patient in the conven-

Table 1.
CLINICAL DETAILS OF THE STUDY GROUPS

	Sex ratio (M:F)	Age (years)	Age at onset (years)	Duration (years)	C-peptide (pmol/ml)
M.C. Insulin group	9:8	54.9 ± 6.9	38.4 ± 7.2	16. 8 ± 3.3	0.23 ± 0.11
Conv. Insulin group	10:5	53.6 ± 7.3	39.3 ± 6.1	15.3 ± 3.9	0.30 ± 0.21

None of the difference between groups were significant statistically.

Table 2.

CHANGES IN BIOCHEMICAL PARAMETERS AFTER TREATMENT (3 YEAR FOLLOW-UP RESULTS)

M.C. Insulin	Initial	Follow-up
Post-Prandial Plasma glucose (mg/dl)	311 ± 85	231 ± 93
HbAI (%)	11.1 ± 1.1	10.0 ± 1.8
Insulin dose (units)	34 ± 12	48 ± 15
Conventional Insulin		
Post-Prandial Plasma glucose (mg/dl)	285 ± 70	226 ± 53
HbAI (%)	10.6 ± 1.7	10.1 ± 1.0
Insulin dose (units)	40 ± 13	55 ± 24

tional insulin treated group progressed to a stage of maculopathy and needed laser photocoagulation in contrast to the M.C. Insulin treated group where none of the patients needed laser therapy.

The mean insulin antibody levels in the two groups are shown in Table 4. There was a significant decrease in the insulin antibody titres in the M.C. Insulin treated group but no decrease was seen in the conventional insulin treated group.

DISCUSSION :

This study shows the follow-up results with treatment using two different insulins of different purity on the course of diabetic retinopathy. The study suffers from certain limitations. Firstly being a long term longitudinal study the study numbers are small. Secondly since fundus photography was not available at the start of the study documentation of lesions had to be done ophthalmoscopically. However, the ophthalmologist was unaware of the treatment modalities. Moreover we have shown in an earlier study, the close correlation between the findings obtained by ophthalmoscopy by an ophthalmologist trained in retinal grading and fundus photography[12].

Despite these limitations the findings obtained in this study are of interest because there is a suggestion that the use of purified

Table 3.

CHANGES IN RETINOPATHY STATUS

Retinopathy status	M.C. Insulin group	Conventional Insulin group	Significance
Regressed	5/17 (29%)	2/15 (13.3%)	p = 0.25
Same	7/17 (42%)	8/15 (53.4%)	p = 0.37
Progressed	5/17 (29%)	5/15 (33.3%)	p = 0.56

Differences between groups not significant (Fischer's exact probability test)

Table 4.

CHANGES IN INSULIN ANTIBODY TITRES

	Insulin Antibody titres (micro-units/ml)		
	Initial	Follow-up	Significance*
M.C. Insulin group (n = 17)	886 ± 125	235 ± 98	p < 0.001
Conv. Insulin group (n = 15)	1056 ± 345	1234 ± 456	N.S.

* Paired 't'test

insulins may have some beneficial effects on the course of diabetic retinopathy. This calls for more detailed studies using larger numbers of patients and using fundus photography and flourescein angiography to confirm these preliminary observations.

The exact mechanism by which purified insulins exert their beneficial effects on the course of microangiopathy is not clear. The reduction of insulin antibody levels is one possibility. In diabetic nephropathy it has been suggested[7] that insulin antibody levels may contribute to the development of nephropathy by formation of immune complexes. However this has not been shown to be important for the development of retinopathy. Obviously more studies are needed to clarify this aspect.

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