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RESEARCH ARTICLE

Effect of Clonidine on Lipid Profile in Diabetic Rabbit Model and Its Interaction with Metformin

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ABSTRACT

This study was designed to investigate the effect of Clonidine on lipid profile parameters like total cholesterol, High density lipids, triglycerides, low density lipids in alloxan-induced diabetic rabbits. Rabbits were divided into six experimental groups: Nondiabetic control group treated with normal saline, Nondiabetic test group treated with Clonidine, diabetic control group treated with normal saline, diabetic test group treated with Clonidine, diabetics treated with Metformin, diabetics treated with Metformin & Clonidine. Treatment with drugs was started on the 3rd day of alloxan treatment (i.e. day 1) and was continued for 30 days. Statistical evaluation was done using student's 't' test & one way ANOVA followed by Tuckey`s post hoc test. 'p' value less than 0.05 was considered statistically significant. But clonidine does not affect any lipid levels in both euglycemic & diabetic rabbits as the p value was found to be statistically insignificant i.e. more than 0.05.

Keywords: Clonidine, diabetes, lipid profile, metformin.

1. INTRODUCTION

Once regarded as a single disease entity, diabetes mellitus is now seen as heterogeneous group of diseases characterized by a state of chronic hyperglycemia resulting from a diversity of etiologies, environmental and genetic factors acting jointly. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels[1].

Six out of top ten countries with the highest rates are in south-East Asia region. India ranked first in the list of countries with the highest numbers of estimated cases of diabetes for 2000 and estimated to be same by 2030[2].

Hypertension is an extremely common co-morbid condition in diabetes, affecting 20 - 60% of patients with diabetes, depending on obesity, ethnicity and age. In type 2 diabetes, hypertension is often present as part of the metabolic syndrome including central obesity and dyslipidemia[3].

If antihypertensive drugs are needed they should be chosen carefully with recognition of their adverse effects and interactions, because many of these agents used to lower blood pressure can affect lipid metabolism adversely.

In any case, if clonidine is used in a diabetic, it may interfere with lipid profile, as clonidine by α2-adrenoceptor stimulation increases growth hormone secretion and decreases insulin secretion from pancreatic β-cells & may also alter the lipid profile. The effects of clonidine on lipid metabolism appear to be variable[4-6].

Hence a need to study the effect of clonidine on lipid profile in diabetics and its interaction with an antidiabetic agent was strongly felt. Therefore, this study was taken up to investigate the effect of clonidine on lipid levels in alloxan-induced diabetic rabbit model and to know the pharmacodynamic interactions of clonidine with a suitable biguanide i.e. metformin. This study will elucidate the steps to be

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taken when clonidine is used concomitantly in diabetics.

2. MATERIALS AND METHODS:

The present study was carried out in Department of Pharmacology at Dr S.C. Government Medical College, Nanded, Maharashtra, India after approval by Institutional Animal Ethics Committee. Handling and care of animals was according to CPCSEA guidelines. Care was taken during the animal study using diabetic animal models include food, water, shelter place (Housing), prevention of infection etc.

MATERIALS

- Experimental animals used in the study: healthy New Zealand rabbits.
- Disposable syringes & needles, oral feeding (blunt curved) needle, mouth gag.
- Glucometer and strips. Lifescan: Johnson & Johnson Co.
- Drugs:

i) Alloxan monohydrate obtained from Loba – Chemie Pvt. Ltd., Mumbai, India.

ii) Metformin obtained from Hoechst India Limited, Mumbai, India.

iii) Clonidine hydrochloride obtained from Unichem Lab. Ltd., Mumbai, India

iv) Vehicle (Normal saline, distilled water).

2.1. Experimental design -

It was a prospective, randomized, analytical, interventional, single blind study. New Zealand rabbits weighing between 1 - 1.5 kg were used for the study. For the experiment, the animals were weighed, numbered and randomly divided into six groups of 6 animals each.

2.2. Induction of Diabetes Mellitus

A single dose (150 mg/kg)[7] of freshly prepared solution of Alloxan monohydrate 5% (dissolved in normal saline) was administered intravenously in lateral marginal ear vein, for induction of type 2 diabetes mellitus in the rabbits. Blood glucose levels were estimated after 24 and 48 hours to confirm the development of diabetes mellitus[8], by the demonstration of blood glucose in the range of 250 - 350 mg/dl[9].

Blood sample for lipid profile parameters estimation was collected from the lateral marginal ear vein[10].

2.3. Method of Lipid Profile Parameters Estimation [11,12]

After overnight fasting 2ml blood was collected in plain bulbs without anticoagulant, from marginal ear veins of all rabbits. Plain bulbs containing blood are kept at room temperature for 30 - 45 minutes for serum separation. After separation of serum from blood, the various biochemical parameters were estimated in the Biochemistry Lab. of medical college. Instrument used for lipid profile estimation was TRANSASIA fully automated random access clinical chemistry analyzer.

Parameters of Lipid profile & method used:

- Total cholesterol: CHOD-PAP method
- Triglyceride: GPO-PAP method
- HDL-Cholesterol: CHOD-PAP method
- LDL-Cholesterol: by Friedwald equation

2.4. Animal groups

Rabbits were divided into six groups as below:

Group 1: Non-diabetic rabbits treated with normal saline.

Group 2: Non-diabetic rabbits treated with clonidine (97.5 µgm/kg)[13,14].

Group 3 : Diabetic rabbits treated with normal saline.

Group 4 : Diabetic rabbits treated with metformin (120 mg/kg) [15].

Group 5 : Diabetic rabbits treated with clonidine (97.5 µgm/kg).

Group 6: Diabetic rabbits treated with metformin (120 mg/kg) and clonidine (97.5 µgm/kg).

2.5. Statistical analysis

The data was expressed as mean ± standard deviation (SD) and Statistical evaluation was done using student's 't' test & one way ANOVA followed by Tuckey`s post hoc test. 'p' value less than 0.05 ($P<0.05$) was considered statistically significant.

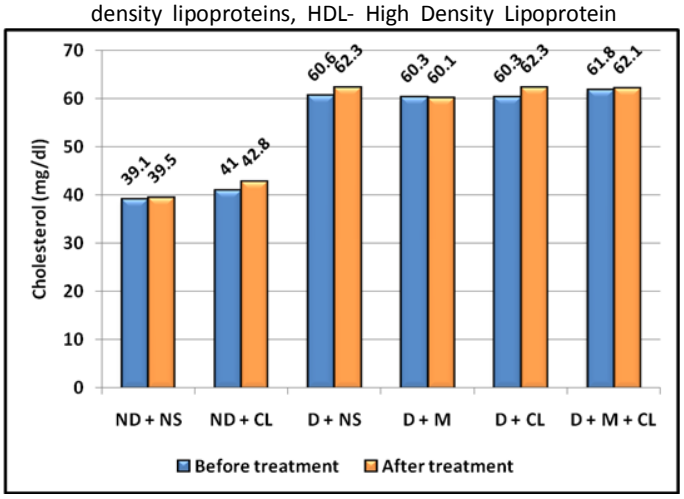
3. RESULTS:

The drugs were administered orally to animals once daily for 30 days. Euglycemic as well as alloxan-induced diabetic animals were subjected for various treatments as mentioned earlier. Lipid profile parameters in different study groups are shown in Table I

	CHOL		TG		LDL		HDL	
	Before	after	before	after	before	after	before	After
1.ND+NS	39.1	39.5	53.5	49.6	2.35	2.3	28.8	27.8
2.ND+CL	41	42.8	60.6	57.8	2.32	2.3	30.6	30.1
3.D+NS	60.6	62.3	138.8	135.3	9.37	9.3	21.3	19.8
4.D+M	60.3	60.1	138.8	137.3	9.81	9.5	19.8	18.8
5.D+CL	60.3	62.3	140.6	139.5	9.54	9.5	21	19.5
6.D+M+CL	61.8	62.1	139.1	137	9.52	9.4	21	19.1

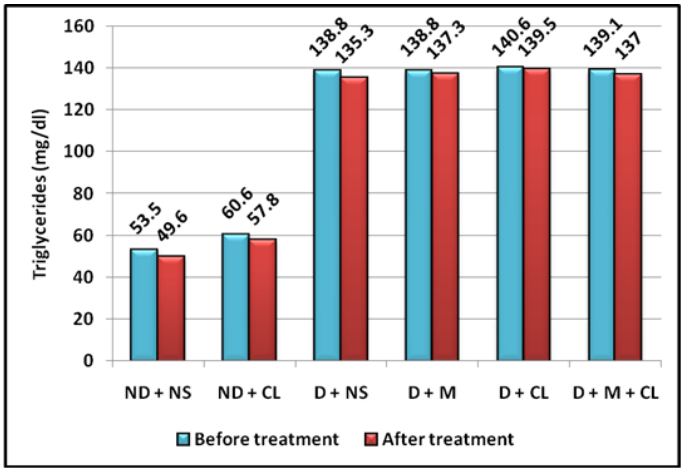
Table I : Lipid profile parameters in different study groups

ND- Nondiabetic, NS- Normal saline, D- Diabetic, M- Metformin, CL- Clonidine, CHOL- Total Cholesterol, TG- Triglycerides, LDL- Low density lipoproteins, HDL- High Density Lipoprotein



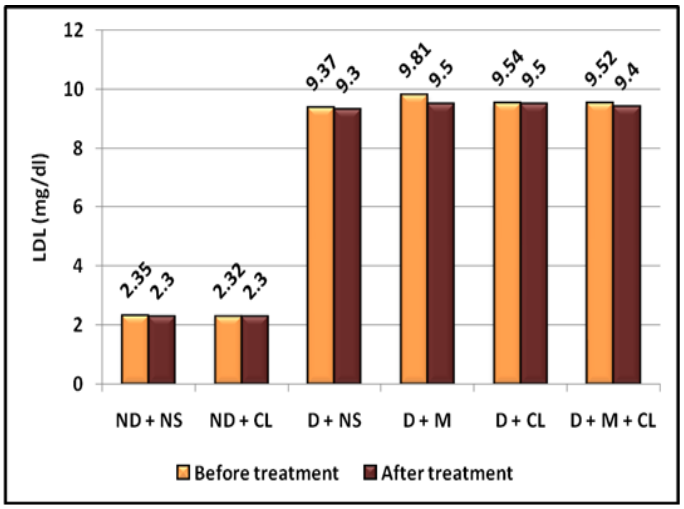
ND- Nondiabetic, NS- Normal saline, D- Diabetic, M- Metformin, CL- Clonidine

Fig 1: Effect of clonidine on Serum Cholesterol levels compared with control



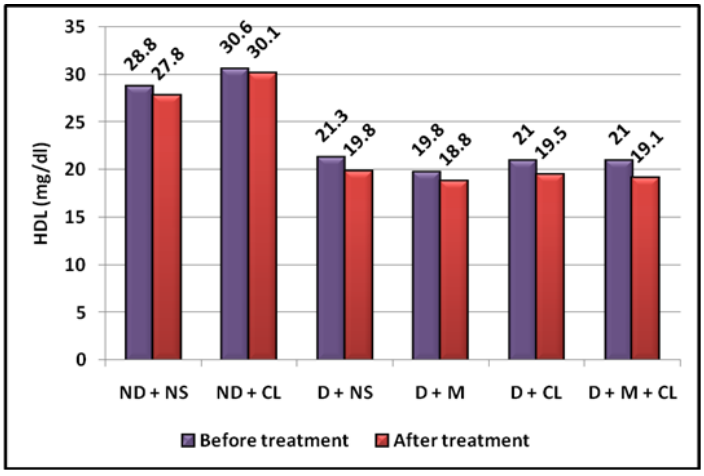
ND- Nondiabetic, NS- Normal saline, D- Diabetic, M- Metformin, CL- Clonidine

Fig 2: Effect of clonidine on Serum Triglycerides levels compared with control.



ND- Nondiabetic, NS- Normal saline, D- Diabetic, M- Metformin, CL- Clonidine

Fig 3: Effect of clonidine on Serum LDL levels compared with control



ND- Nondiabetic, NS- Normal saline, D- Diabetic, M- Metformin, CL- Clonidine

Fig 4 : Effect of clonidine on Serum HDL levels compared with control

In general, hyperglycemia in diabetes mellitus is associated with elevated serum total cholesterol, triglyceride, LDL levels & decreased HDL levels, which was observed in the present study.

But clonidine does not affect any lipid levels in both euglycemic & diabetic rabbits as the p value found statistically insignificant i.e. more than 0.05 as shown in Figs. 1 to 4

4. DISCUSSION:

Clonidine, a known antihypertensive, produces fall in insulin levels and increase in growth hormone secretion. This study was conducted to explore the outcome of these actions i.e. hyperlipidemia or dyslipidemia. There are scanty reports mentioning the actions of clonidine on lipid parameters also.

The effect of clonidine on lipid metabolism was found statistically not significant, but in some studies clonidine is grouped under an antihypertensive with favourable effects on serum lipids[4]. In some earlier studies clonidine was found to cause significant reductions in high density lipoprotein cholesterol, apolipoproteins A-I and A-II but was neutral on all other lipids, lipid subfractions & apolipoproteins and also clonidine did not significantly alter any of the lipid ratios[5]. In yet another study it was observed that when clonidine given intra-cerebro-ventricularly induces hyperlipemic and hyperglycemic effects[6]. In present study no such effects on lipid levels were observed.

Further studies are required to understand the exact mechanism of this interaction and its clinical implications.

5. CONCLUSION:

The results of present study conclude that clonidine has no effect on lipid profile parameters in both

euglycemic and diabetic rabbits, it also does not interact with metformin to reduce its hypoglycemic effect. If these findings are true to human beings, Clonidine may be used in Type II diabetes patients on metformin therapy. However, further studies are needed to understand its clinical implications.

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Conflict of Interest: None Declared

