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To Evaluate the Therapeutic Efficacy of Hydroxychloroquine in Atherosclerotic Arterial Disease - Effect On Carotid Intima Media Thickness

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Abstract **Original Research Article**

Background: Carotid Intima Media Thickness (CIMT) found to correlate with atherosclerosis burden and predict cardiovascular (CVD) risk. As immune mechanism is involved in pathogenesis of atherosclerosis, efficacy of immune modulator Hydroxychloroquine (HCQS) is evaluated in its management. ***Material and Method:*** Comparative clinical efficacy of Atorastatin, Atorvastain plus HCQS, and HCQS was evaluated, based on CIMT regression, in patients with associated CVD risks. ***Results:*** 114 patients completed the study, were clinically evaluated in three groups: Group-1 (Atorvastatin), Group- 2 (Atorvastatin plus HCQS) and Group-3 (HCQS). Majority of patients were in 51–70 age. Major diseases with CVD risk were diabetes mellitus, hypertension, CAD, obesity or in combinations. As CIMT measurement correlates with CVD risk, its regression measured revealed appreciable CIMT regression in Group -2 and Group–3 than Group – 1 at 12 2 months. Diabetic patients with or without comorbidities had shown better regression than others. CIMT regression in obese subset was unremarkable. ***Conclusion:*** HCQS with statins was almost as effective as when given alone in reducing CIMT, hence useful in reduction in CVD risk. HCQS may be tried as an adjuvant with statin in atherosclerosis CVD risks management

Keywords: CIMT, Hydroxychloroquine, Immunomodulators, Statins.

INTRODUCTION

Considerable evidences suggest role of inflammation in all stages of atherosclerosis i.e. from endothelial dysfunction to plaque rupture [1]. Increasing inflammatory biomarkers in blood indicate progression of atherosclerosis and correlate with progression of cardiovascular risks. Similarly, Carotid Intima Media Thickness (CIMT) found to correlate with overall estimate of atherosclerosis burden and predict cardiovascular (CVD) risk. CIMT assumes that atherosclerosis being a systemic disease; it can be measured interchangeably between carotids and coronaries. It also predicts CVD related clinical events in subjects without clinical evident disease [2] and CVD risk reduction with regression of CIMT by statins [3-5]. But detrimental outcome were reported with statins e.g. breast cancer with pravastatin [6], diabetes mellitus with rosuvastatin [7], hemorrhagic stroke with atorvastatin [8] but subsequent verification did not substantiate these occurrences.

Immune cellular mechanism in the pathogenesis of atherosclerosis is well established, but role of immune-modulators remain speculative in its treatment. Hydroxychloroquine (HCQ), an anti-inflammatory drug, has been shown to have multiple pleiotropic actions relevant to atherosclerosis [9]. Though many immune modulators in various clinical trials have shown beneficial effects in CVD, HCQS has not been tried in the treatment strategy of atherosclerosis.

Present study is undertaken to assess clinically, if HCQS – immune modulator- well prescribed in connective tissue disorders, can be efficacious in treatment alone or as an adjuvant.

MATERIALS AND METHODS

This prospective, randomized and non-intervention study was carried out in Tertiary Referral Hospital in Himachal Pardesh (India). Patients were allotted in three groups. Every third male and every third female was included in each group in random manner.

Duration of the study was from Jul 2014 to Mar 2017.

Ethical Issue

The research was approved by the Ethical Committee of the institution and conducted as per its laid down norms.

Participants

On enrolment in the study, each patient was informed about the nature of the study and, if agreed, consent taken and a Participation Number allotted.

Inclusion criteria

Diabetes Mellitus type 2 (DM Ty 2); Hypertension, Coronary Artery Disease (with effort angina), Obese with BMI ≥30 Kg/m², Dyslipidemia; Metabolic Syndrome, Transient Ischemic Stroke, Asymptomatic Carotid / subclavian arterial bruit and Family history of premature acute cardiac event, stroke.

Exclusion criteria

Chronic Heart Failure (CHF), terminally ill patients, Chronic Kidney Diseases, epilepsy, psychotic illnesses, muscle disorders (nutritional, hereditary, vascular, neurogenic, traumatic or metabolic / drug induced), Retinal diseases and patients with previously observed adverse effects to HCQS.

Total 257 patients were taken in for study (Table - 1). At the time of enrolment, clinical examination was carried out particular in reference to central nervous system (CNS), Ophthalmological, especially, retinal examination and cardiovascular system (CVS).

Relevant laboratory tests i.e. haematological & biochemical parameters and Erythrocytic Sedimentation Rate (ESR) & C - reactive protein (CRP) were performed. CIMT measured by Colour Doppler on enrolment and subsequently three monthly. Patients were cautioned to report immediately on occurrence of any adverse reaction, especially relating to vision.

Table-1: Participants in Study

Total patients included in study	257
Total patients excluded from study	143
(a) Did not report since within one month of initial inclusion	116
(b) Died:	2
• Acute Coronary Event	2
• Intracerebral Hemorrhage	1
• Septicemia in DM Ty 2	22
(c) Irregular treatment, shifted outside the area, did not report for or unable to follow up	
Total Patients followed up till date	114

(Table: 1. Depicting patients initially enrolled in the study and completed the study)

Patients were divided randomly in three groups (Gp). Group -1 (Atorvastatin group) of 87 patients (male 54 and female 33); Group – 2 (Atorvastatin + HCQS group) of 86 patients (male 55 and female 31) and Group – 3 (HCQS group) of 84 patients (male 52 and female 32) also depicted in Table 2 & 3. During study period 143 patients left the study or were excluded because of irregular follow up and medication (Table 1 & 2).

Table-2: Distribution of patients Age - wise

Age(Years)	Gp-1	MF	Gp-2	MF	Gp –3	MF	TotalMF	
40 – 50	-	1(1)	-	1(1)	-	2 (1)	-	4 (3)
51 - 60	2	3(2**)	3	5(1)	3	5 (3)	8	13 (6)
61 - 70	24(13^)	16(11)	27(13*)	18(11)	26(9**)	20(11)	77(35)	54(33)
≥ 70	28(19*)	13(9)	25(17)	7(4)	23(15)	5 (2)	76(51)	25(15)
Total	54(32)	33(23)	55(30)	31(17)	52(24)	32(17)	161(86)	96(57)

(Note: Figures in brackets denote patients who were excluded from study
*Deaths due to Acute Coronary Event, ** Deaths due to Intracerebral Hemorrhage,
^ Death due Septicemia in Diabetic patient)

Table-3: Distribution of patients Group and Sex - wise

Patients	Group -1 (Atorvastatin Gp)	Group-2 (Atorvastatin + HCQS Gp)	Group-3 (HCQS Gp)	Total
A. Included	87	86	84	257
Male	54	55	52	161
Female	33	31	32	96
B. Excluded	55	47	41	143
Male	32 (* 1 &^1)	30 (*1)	24 (**1)	86
Female	23 (**1)	17	17	57
C. Study Patients	32	39	35	114
Male	22	25	28	75
Female	10	14	15	39

(Note: *Deaths due to Acute Coronary Event ** Deaths due to Intracerebral Haemorrhage
^ Death due Septicemia in Diabetic patient)

Follow up Protocol

(1) Subjective symptoms: It is measured in terms of symptomless duration of exertion as:-

- Age related performance of daily routine work, especially, with symptoms suggestive of coronary ischemia; peripheral vascular insufficiency or giddiness / syncope.
- Symptoms suggestive of Cerebrovascular event
- Routine climbing hilly gradient near his house and to work place.
- Walking without gradient.
- Any other tolerable physical activity.

(2) Monthly clinical and ophthalmological examination, especially, to detect HCQS or disease related improvement.

(3) Monthly relevant biochemical, haematological tests, electrocardiogram (ECG) & CRP

(4) Three monthly CT recording of CIMT.

Study End – points

- Symptomatic improvement in effort tolerance (as mentioned in "follow – up protocol") at the end of study.
- CIMT regression from baseline.
- Retinal / visual changes during study.
- Adverse effects which required hospitalization.
- Fatal or non-fatal Stroke, Acute CAD event and death during study period.

RESULTS

This is a small study to explore the clinical efficacy of HCQS in atherosclerotic disease. Total 257 patients (male 161 and female 96) were enrolled and randomized into three groups: Gp–1 (Atorvastatin), Gp–2 (Atorvastatin+HCQS) and Gp–3 (HCQS). 143 (male 86 & female 57) were excluded (Table – 1 & 2). 116 patients never reported after inclusion in the study; 5 patients died and 22 were excluded due to poor follow up compliance (Table – 1). Finally, 114 patients completed the study i.e. Gp – 1: 32 (male 22 & female 10), Gp – 2: 39 (male 25 & female 14) and Gp – 3: 43 (male 28 & female 15). Male to female ratio was 1.92:1 [in (Gp -1) 2:2, in (Gp – 2) 1.79:1 and in (Gp – 3) 1.87:1]. Majority of patients were in age 61 – 70 i.e. 16, 21 and 26 in each respective group. Patients under study found to have diseases depicted in (Table – 4).

Gp-1 patients were given Atorvastatin 80 mg OD daily, Gp – 2 patients Atorvastatin 80 mg plus HCQS 400mg OD and Gp – 3 HCQS 400mg OD. Every medication was advised to be taken after dinner. Therapy for coronary heart disease (CAD); hypertension, DM and / or any chronic disease, if any, continued. All patients were followed up, initially fortnightly then monthly.

Blood glucose, HBAIc and hypertension were fairly well controlled (Tale-5). Effort tolerance improved in all groups but more in Gp-2 and Gp-3 as compared to Gp-1 (Table-6). Weight management and exercise programmes recommendations have shown poor outcome throughout the study period (Table-7). Significant positive associations of CIMT measurements were found for higher age, male sex, BMI, HTN, total cholesterol, DM, and a previous history of myocardial infarction or stroke. CIMT measurement in male was more than in female. It was found that greater the CIMT measurement values were associated with better regression and vice versa. There was appreciable CIMT regression in all groups in both sexes, except elderly

Table-4: Diseases – wise distribution of Patricipants

Sr No.	Diseases	Number	Percentage	GP – 1	Gp - 2	Gp - 3
1.	CAD	17	14.91	5	6	6
2.	HTN	19	16.67	5	7	7
3.	DM	14	12.28	4	4	6
4.	DM & HTN	8	7.02	2	3	3
5.	DM & CAD	9	7.89	4	3	2
6.	HTN & CAD	11	9.65	3	3	5
7.	DM, CAD & HTN	5	4.39	1	2	2
8.	OBESITY	13	11.40	4	4	5
9.	OBESITY, HTN CAD & DM	2	1.75	-	1	1
10.	OBESITY & DM	5	4.39	1	3	1
11.	OBESITY & HTN	7	6.14	2	1	4
12.	DM & PVD	1	0.88	-	-	1
13.	TIA & HTN	1	0.88	-	1	-
14.	RECURRENT SYNCOPE	2	1.75	1	1	-
	TOTAL	114		32	39	43

Table-5: Hypertension control during study period

Groups	Patients	Mean BP mmHg Before Study	Mean BP mmHg After Study
Gp– 1	13	168±10/ 96±8	130±8/ 88± 4
GP - 2	18	170±10/ 98±8	136±8/88 ± 4
Gp – 3	22	138±6/ 80±4	138±6/80 ± 4

(Mean BP *After Study:* achieved at the end of study)

Table-6: Effort Tolerance at the end of Study

Groups	Patients	NYHA Class (pre-treatment)	NYHA Class (Post therapy)
Gp – 1	13	I - II	Equivocally improved
Gp – 2	16	I - II	Improvement appreciable
Gp – 3	13	I – II	Improvement appreciable

(NYHA Class: New York Heart Association Classification. Improvement in NYHA Class Pre and Post treatment is purely subjective.)

Table-7: Weight/ BMI Measurement in Obese Patients

Groups	Males (Obese)	Mean Weight/BMI at enrolment	Mean Weight/BMI at 3 months	Mean Weight/BMI at 6 months	Mean Weight/BMI at 12 months
Gp – 1	5	69.2±13.2/32.5 ± 5.4	70±12.5/32.4 ± 4.8	69.6±12.6 / 32.4±4.7	69.2±12.6/ 32.3±4.4
Gp – 2	4	68.4±11.4/31 ± 5.5	68.3±11.2 /31 ± 5.4	68.3±11.3 / 31±5.3	68.4±11.2/ 31.0±5.2
Gp – 3	5	66.7±12.3 /30.4 ± 6.2	66.5±12.4/ 30.4±6.3	66.0±10.3/ 29±7.2	65.2±10.2/ 29±6.5
Groups	Females (Obese)	Mean Weight/BMI at enrolment	Mean Weight/BMI at 3 months	Mean weight/BMI at 6 months	Mean weight/BMI at 12 months
Gp – 1	2	66.2±11.2/30.5 ± 6.4	65.9±11.5/30.6 ± 6.5	65.6±11.3 / 30.2±4.6	65.2±11.4/ 30.3±4.4
Gp – 2	5	67.3±10.5/29 ± 6.5	67.3±10.5 /29 ± 6.4	66.8±10.8 / 29±5.2	66.4±10.2/ 29.0±5.0
Gp – 3	6	67.2±12.8 /29.2 ± 7.4	67.6±13.0/ 29.45 ± 7.3	67.0±12.7/ 29. 2 ± 7.0	66.0±11.8/ 29±6.7

(Note: BMI: Body Mass Index)

Patients (> 70 years) where regression was equivocal. CIMT regression was more appreciable in males than females. Atorvastatin (Gp-1) and HCQS (Gp-3) arms have shown almost equal CIMT regression, whereas Atorvastatin plus HCQS arm (Gp – 2) regression was more appreciable than other groups (Table – 8). CIMT regression in obese patients was not appreciable. Diabetic patients with or without other co-morbidities have shown better CIMT regression than in other co- morbidities associated with CVD risks. Secondly, CIMT regression was noticed to be better in Gp–2 diabetic patients, despite whether DM was adequately controlled or not, except in DM with obesity. HCQS therapy was tolerated well by all participants.

Table-8: Carotid Intima Media Thickness: Measurements

Groups	Patients Males	Mean CIMT at enrolment	Mean CIMT at 3 months	Mean CIMT at 6 months	Mean CIMT at 12 months
Gp – 1	22	0.87 ± 0.04	0.86±0.02	0.86± 0.06	0.86 ± 0.02
Gp – 2	25	0.86± 0.05	0.85±0.02	0.85 ± 0.05	0.85±0.02
Gp – 3	28	0.88± 0.06	0.87±0.04	0.87 ± 0.04	0.87±0.05
Groups	Patients Females	Mean CIMT at enrolment	Mean CIMT at 3 months	Mean CIMT at 6 months	Mean CIMT at 12 months
Gp – 1	10	0.86 ± 0.03	0.86±0.04	0.86±0.08	0.85±0.04
Gp – 2	14	0.87± 0.03	0.87±0.06	0.86±0.03	0.86±0.02
Gp – 3	15	0.87± 0.02	0.86±0.07	0.85±0.02	0.85±0.07

Adverse Effects: Following adverse effects were observed during Study period:

Ten patients had anorexia, 2 nausea / vomiting, 01 abdomen pain with diarrhea and 01 generalized weakness. These disappear after transient cessation of HCQS therapy. There was no case of alteration of vision, colour perception or retinal changes. These side effects of HCQS did not required hospitalization. Muscular aches and pain associated with mild rise in hepatic enzymes were noticed in 3 patients of Gp – 2. Symptoms got abetted after temporary cessation of Atorvastatin and not HCQS.

DISCUSSION

Atherosclerosis is a chronic inflammatory systemic condition. Oxidized and enzymatically modified Low Density Lipoproteins (oxLDL) attract immune competent cells which produce proinflammatory cytokines [9], thereby exhibiting proinflammatory and immune stimulatory properties. Oxidized phospholipids [10], apolipoprotein B [11] and Heat Shock Proteins (HSPs), especially HSP 60, HSP70 & 90 [12] also play important role in its pathogenesis.

Plaque rupture is also mediated through the effect of proinflammatory cytokines and chemokines on fibrous cap in atherosclerotic lesion. Atherosclerosis due to any mechanism i.e. induced by modified products of lipids, other types of inflammations and autoimmune diseases has relationship with CVD high risk [13-15].

CIMT measurement and atherosclerosis burden

CIMT seems to correlate with overall estimate of atherosclerosis burden and used as surrogate endpoint to predict CVD risk related clinical events in subjects even without clinical evident disease [2]. CIMT assumes that atherosclerosis being a systemic disease; it can be measured interchangeably between carotids and coronaries. Intima-media thickness or plaque values of more than 0.9 mm by European Society of Cardiology (ESC) or over the 75th percentile by American society of Echocardiography (ASE) should be considered abnormal and associated with target organ damage. Carotid artery ultrasound scan for CIMT is the method of choice for searching asymptomatic atherosclerosis. It is a non-invasive, safe, easily performed, reproducible, sensitive, relatively inexpensive and widely available method for detection of early stages of atherosclerosis and is accepted as one of the best methods for evaluation of arterial wall structure.

Basis of this study: This study is conceived based on observations from various trials that:

- Statins also act immune modulators [16, 17]. Statins in addition to HMG CoA Reductase inhibitors were also found to exhibit anti - inflammatory properties.
- Statins through immunomodulation, directly interfering with major histocompatible complex MHC class II presentation [16] and efficacious in patients with raised high sensitive CRP but normal LDL [17]. It is difficult to establish benefit of statins whether due to reduction of LDL or anti – inflammatory response or both.
- Methotrxate treatment in Rheumatoid Arthritis (RA) patients reduces CVD [17, 18].
- Other anti – inflammatory therapies studied in various trials like IL - 1β inhibition [19], Annexin A5 an anti – thrombotic plasma protein [20], inhibition of Lp-PLA activity with darapladib [21], anti – TNF had beneficial effect in decreasing CVD [22].

- Immunomodulator therapy was shown to be effective as immunization with modified form of LDL [23].
- At least in human beings, no anti -inflammatory or immune modulatory therapy available or tried till now in treatment of CVD though it is known, atherosclerosis as risk factor for CVD for long time.

In this study HCQS, an immunomodulator, widely used in rheumatic diseases as 'add – on', is evaluated for its beneficial effects on CIMT regression Vis – a – Vis in the reduction of atherosclerosis risk for CVD. Data in this, though brief study, HCQS supplement with Atorvastatin has shown favourable CIMT regression both subjectively and clinically. Results of HCQS therapy alone in CIMT regression just approached those of statins.

Patients reported subjectively improved exercise tolerance, less episodes on physical efforts related generalized weakness, better performance in routine activities and improvement in NYHA grade. Contribution of HTN and DM control with clinical improvement in symptoms of these patients cannot be ignored. But in most of the patients HTN and DM were control even before enrolment in the study. It seems statin and / or HCQS had additional benefits and could be related to the CIMT (atherosclerosis) regression. Statins, in addition to HMG CoA Reductase inhibition, also act as immunomodulators [16, 17] exhibit anti – inflammatory properties. These benefits of statins due to either LDL reduction or anti – inflammatory response or both are difficult to establish. HCQS has been shown to have multiple pleiotropic actions relevant to atherosclerosis [18]. Beneficial effects of HCQS (Gp–3) and in HCQS plus Atorvastatin (Gp–2) seem to be due to immunomodulation, in that decreasing cellular burden in CIMT atherosclerotic area resulting in reduced synthesis of pro - inflammatory chemokines and cytokines and hence LDL formation in situ. It is inferred that HCQS alone or in combination with statins delay the plaque rupture also by reducing inflammation in fibrous cap. Clinical efficacy by immunomodulation of atherosclerosis was also documented in various studies [17-23]. HCQS also improves endothelial dysfunction and Nitric Oxide (NO) from endothelial cells [18, 25, 26], and decreases inflammatory markers [17]. Endothelial integrity and NO availability are important in the maintenance of vascular tone, inflammation control, and prevent smooth muscle cell proliferation and migration, and thrombogenesis, fibrinolysis [27] and eventual downstream worsening of atherosclerosis.

Data in this study shows diabetic patients with or without other co-morbidities, except obesity, have shown better CIMT regression than others. Though its exact mechanism in CIMT regression is not clear, yet it can be formulated based on some studies. HCQS increases insulin sensitivity both in human beings and animals [28, 29], as when added to sulfonylurea, it has improvement in their glycemic control with a reduction of 1.02% to 3.3% in their HbA1C [30, 31]. SLE and RA patients when administrated HCQS had shown significant reduction in triglycerides (TGs) and apolipoprotein CIII, LDL [32-35]. These may explain better CIMT regression in diabetics than in other patients.

Though HCQS increases insulin sensitivity yet in obese patients, either isolated or with other comorbidities, beneficial effects were not remarkable in all groups (Gp – 3, Gp – 2 and also in Gp – 1). No explanation can be affordable in this condition.

HCQS is associated with various adverse effects, especially ophthalmic, but in this study no such major adverse effect was encountered necessitating permanent cessation of HCQS. Other adverse effects were infrequent requiring temporary cessation of HCQS which was resumed subsequently starting from low dose and attaining full dose without recurrence of these effects.

Considerations during CIMT measurement

When considering CIMT measurement as main diagnostic tool, clinician must take into consideration the followings aspects:

- CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first atherosclerotic cardiovascular disease event [36]. Serial CIMT to assess progression or regression in individual patients are not recommended [37].
- The main problem in interpreting CIMT results from clinical trials is the differences in measurement methodology. These are resolved to greater extent by preferring B-mode than M-mode imaging, by equipment settings (focus depth, frame rate, gain setting, discourage use of zoom function), inclusion of carotid bifurcation in imaging, requiring at least 10mm straight arterial segment.
- There is steady increase in CIMT with advancing age and more in males than in females.
- CIMT is a marker of subclinical atherosclerosis (asymptomatic organ damage) and should be evaluated in every asymptomatic adult or hypertensive patient at moderate risk for CVD.

Limitations of the Study

- Small size of study
- In this study only common carotids were selected for CIMT evaluation. Problems in interpreting CIMT results arise due to differences in measurement methodology. The discrepancies are: the precise definition of the investigated carotid segment, the use of mean or maximal CIMT, the

measurement of near and far wall or only far wall CIMT, the view at a single or different angles, employing manual tracking or an automated software, including carotid plaques or not and uni- or bilateral measurements.

- Which carotid segment should be considered abnormal, is not yet settled?
- Age and sex related variations in CIMT which increases with age
- Increase in CIMT can also result from non-atherosclerotic processes i.e. smooth muscles hyperplasia, fibrocellular hypertrophy and arteriosclerosis in response to wall remodelling.
- Though CIMT is an important atherosclerotic risk marker but cannot be accepted as a risk factor and patient should not be subjected to treatment based on this finding [36].

CONCLUSION

Atherosclerosis being a immune mediated systemic inflammatory disease, it is suggested that immune modulator HCQS therapy can be considered in management of atherosclerosis CVD risk subjected to the confirmation of its efficacy in large therapeutic trials.

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