Effects of Hydroxychloroquine as an Add-on to Conventional Therapy in Patients with Diabetic Nephropathy:A Randomized Controlled Trial

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Abstract

Background: Hydroxychloroquine (HCQ) has been found to have antithrombotic, lipid-lowering and glucose-lowering properties that make it useful in treating a variety of chronic diseases, including rheumatoid arthritis and systemic lupus erythematosus. Recently various study also showed its anti proteinuric andrenoprotective effects. To evaluate the effecacy of HCQ as an add on to the conventional therapy of Diabetic Nephropathy (DN).

Materials and methods: This open label randomized controlled trial was conducted at the Chittagong Medical College Hospital in Chattogram at the Nephrology Department. Sixty patients of DN were enrolled as per selection criteria into two groups, in one group 30 patients were started HCQ (100 mg twice daily) along with conventional treatment of DN (Experimental group). In other group 30 patients were started with conventional treatment without HCQ (Control group). They were followed up after 3rd and 6th month of initiation of the treatment. Both groups were followed upfor any significant changes in their renal function, proteinuria, glycaemic status and lipid profile.

Results: At the end of six months there was almost 8.9% reduction of serum creatinine in experimental group while it increased in control group around 22.2% both of which were significant (p<0.001). In contrast, eGFR increased by almost 9.9% in experimental group and decreased by 15% in control group which were also statistically significant (p<0.001).The proportion of patients who had >30% reduction of proteinuria after six months in the experimental and control groups was 50% and 6.7%, respectively (p<0.001). After 6 months, serum cholesterol declined significantly (24.76±30.82; p <0.001)in the experimental group and it was not significant in the control group (8.19±30.82; p >0.15). Glycaemic status also significantly improve in experimentalgroup but not in control group. No major adverse events were observed in the two groups.

Conclusion: These results were supportive of the renoprotective effects of HCQ in patients of DN. Therefore, we concludedthat HCQ can be an option in regression of DN in patients of DM.

Key words: Diabetic nephropathy; Hydroxychloroquine; Glomerular Filtration Rate (GFR); Serim creatinine.

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Introduction

Diabetes Mellitus (DM) is one of the major non-communicable disease. Most of the people with diabetes are livingin low and middle income countries. The International Diabetes Federation projected that prevalence of DM in Bangladesh will increase to more than 50% by next 15 years.[1,2]

About 50% of all End Stage Renal Disease (ESRD) cases are caused by Diabetic Nephropathy (DN) one of the chronic microvascular consequences that is linked to significant morbidity and death. As a result, the cost of renal replacement treatment and healthcare services rises.[3-5] The etiology of DN involves several pathophysiologic processes, although the underlying mechanisms are still poorly understood.[6] Advanced renal insufficiency, hypertension, and proteinuria that is generally defined as urine albumin excretion more than 30 mg/24 hours and it is the hallmarks of diabetic kidney disease

Strict blood pressure and glucose management, together with Renin-Angiotensin System (RAS)

suppression with the use of Angiotensin Receptor Blockers (ARBs) and Angiotensin-Converting Enzyme Inhibitors (ACEIs) are the mainstays of current DN treatment strategies.[7] Nevertheless, DN patients treated with ACEIs or ARBs experienced 15% or higher yearly renal event rates and were not totally cured of proteinuria.[8] To lessen the burden on DN patients, further therapies that can improve proteinuria are thus required.

In recent years, there has been a significant advancement in our knowledge of the pathophysiologic mechanisms that contribute to Diabetic Kidney Disease (DKD). These days, it is understood that the development and progression of diabetic complications are closely linked to both chronic low-grade inflammation and the innate immune system's activation, particularly the elevation of proinflammatory cytokines that occurs in diabetes mellitus.

It has recently been discovered that Hydroxychloroquine (HCQ), a well-known immunomodulator that is frequently used to treat inflammatory or autoimmunologic illnesses, is a safe and promising antiproteinuric drug that can be utilized to treat IgA nephropathy. When combined with regular RAASi medication, HCQ significantly decreased proteinuria and increased the incidence of proteinuria remission in less than six months.[9,10] HCQ increases insulin sensitivity and prevents insulin breakdown.[11] These antimalarial drugs have a positive impact on glucose levels and the serum lipid profile.[12,13]
With this background we proposed to conduct this study to assess whether HCQ could raise eGFR despite receiving an ACEI or ARB in patient with DN.

Materials and methods

This open-label randomized controlled trial was conducted in the Department of Nephrology, Chittagong Medical college Hospital (CMCH), Chattogram during the period from January 2019 to December 2019. Patients were selected purposively as per inclusion and exclusion criteria.Inclusion criteria were Type 2 DM with diabetic nephropathy upto stage 4 CKD,Type 2 DM with urinary ACR >30 mg/gm and age between 30-80 years.Exclusion criteria wereType-1 DM, non diabetic kidney disease with DM, DKD patients with history of coronary artery disease or congestive heart failure or QT interval more than 450 milliseconds (ms), pregnant or lactating women or any malignancy and patients who refused to participate.

Approval was taken from the Ethical and Research Committee of Chittagong Medical College Hospital (CMCH). Selected patients of DN attending the OPD of Nephrology Department, CMCH during study periodwere randomized into two group. Experimental group received Tab. HCQ, 100mg twice daily, along with the conventional treatment of DN (ARB). Patients of Control group received conventional treatment of DN (ARB) without HCQ. Each patient had a baseline or enrolment visit followed by 3rd month and 6th month visit.Patients' baseline characteristics, such as age, sex, educational level, and clinical and biochemical information were recordedat start of study and following parameters were investigated in each follow-up along with any toxic effects of the study drug: blood sugar-Fasting and Post prandial glucose, HbA1c, Urine Albumin Creatinine Ratio (uACR) ECG, Serum creatinine level, Serum lipid profile and urine routine and microscopic examination. Lipid profile was included serum cholesterol, serum triglyceride, High Density Lipoprotein-Cholesterol (HDL-C) Low Density Lipoprotein-Cholesterol (LDL-C).

All clinical data andlaboratory reports were re-coded in a predesigned data sheet an analyzed by using SPSS version 23. Data were analyzied as per intention to treat principle. To find out the treatment effect of numberneed to treat was calculated by taking reduction of proteinuria >30% from baseline to month 6 as significant reduction. Statistical significance was defined as $p < 0.05$ and confidence interval set at 95% level.

Results

Table I Baseline clinical and biochemical characteristics of the participants by study groups

Variables (Unit)		Experimental Group (n=30)	Control group (n=30)	p value
Age (Years)		54.13 (±11.43)	51.53 (±11.22)	0.37*
Sex	Male	18 (60.0%)	15 (50.0%)	0.43†
	Female	12 (40.0%)	15 (50.0%)	
H/O Hypertension	Yes	23(76.0%)	25(83.3%)	0.52 †
	No	7(23.3%)	5(16.7%)	
Duration of DM (Years)		<5 years	6(20.0%)	3(10.0%)
	6-10 years	15(50.0%)	21(70.0%)	0.37 †
	11-15 years	6(20.0%)	5(16.3%)	
	>16 years	3(10.0%)	1(3.3%)	
CKD stage	2	6(20.0%)	10(33.3%)	
	3	17(56.7%)	15(50.0%)	0.48 †
	4	7(23.3%)	5(16.7%)	
BMI (kg/m^2)		26.67±1.90	25.21±3.32	0.09*
SBP (mmHg)		133±13	135±14	0.10*
DBP (mmHg)		78±7	81±7	0.25*
FBS (mmol/l)		8.71±3.05	8.19±3.41	0.54*
Blood sugar 2hrs PP (mmol/l)		11.98±3.99	11.62±4.2	0.73*
Hemoglobin A1c (%)		8.22±1.34	7.68±1.86	0.19*
Serum creatinine (mg/dl)		1.79±0.79	1.53±0.76	0.18*
eGFR (ml/min per 1.73 m^2)		41.50±15.88	49.96±17.98	0.18*
uACR (mg/gm)		499 (127-1255)	189 (70-1093)	0.17††
Serum cholesterol (mg/dl)		205.27±47.67	191.63±56.42	0.32*
Serum triglyceride (mg/dl)		186.20 ±73.21	187.83±80.39	0.88*
Serum HDL-C (mg/dl)		38.10 ±7.49	38.53±7.41	0.82*
Serum LDL-C (mg/dl)		121.33±30.41	114.97±37.29	0.47*

Data are expressed as frequency (Percentages), mean±SD and median (Interquartile range), p values were derived from †Chi-square test, Independent sample t test, Mann-Whiteny U test††.

Mean age was just above 50 years and male predominate in both group. However, both the groups were similar with respect to their age and sex distribution.Majority of the patients in both the groups had history of hypertension. Moreover, DM was present for 6-10 years in majority of the patients in both groups. Regarding CKD stage, predominant stage was stage 3 in both groups. Both the groups were comparable with respect to presence of hypertension, duration of DM, stage of CKD, BMI, SBP and DBP at baseline. The two groups did not differ for baseline glycemic status, serum creatinine, eGFR, uACR and lipid profile significantly (Table I).

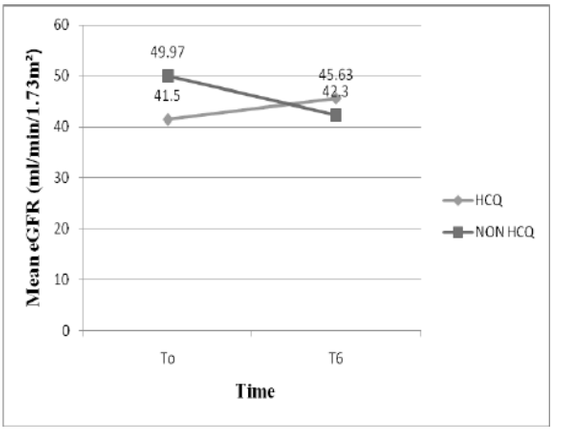

Figure 1 eGFR mean variation between Experimental group and Control group from baseline to 6th month

In experimental group, eGFR was increased (41.50±16.88 to 45.63 ±17.18 ml/min/1.73 m^2) and in control group, it was decreased (49.97±17.99 to 42.30±12.87 ml/min/1.73 m^2) from baseline to 6 month. Comparison of changes between both groups were statistically significant (p<0.001) (Figure 1).

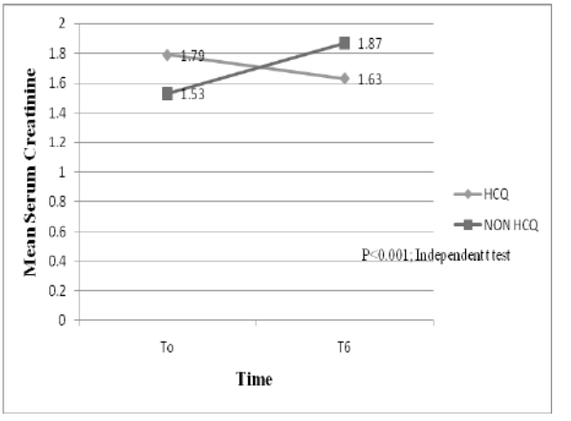

Figure 2 Serum Creatinine Mean variation between Experimental group and Control group from baseline to 6th month

In experimental group, serum creatinine was decreased (1.79±0.79 to1.63±0.73 mg/dl) and in control group, it was increased (1.53±0.76 to 1.87±1.15 mg/dl) from baseline to 6 month. Comparison of changes between both groups were statistically significant (p<0.001) (Figure 2).

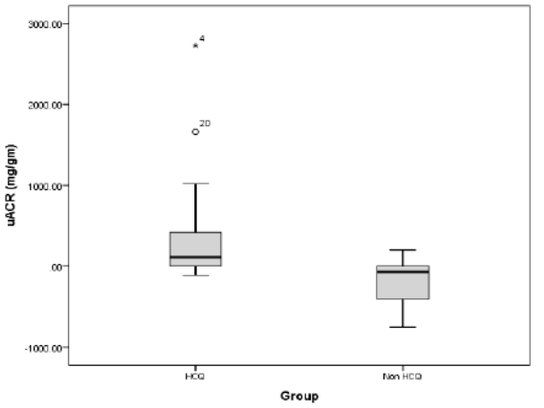

Figure 3 uACRvariation between Experimental group and Control groupfrom baseline to 6th month

uACR was decreased in experimenta group (median changes 109.3 mg/gm) and increased in control group (Median changes 70.2 mg/gm) from baseline to 6 month. Comparison of changes were statistically significant (p<0.001) (Figure 3).

Table II Comparison of changes of Variables from baseline to month 6 in between Experimental group and Control group (n=30)

Variables (unit)	Experimental Group		ControlGroup		p value*
	At Baseline	At month 6	At Baseline	At month 6	
FBS (mmol/l)	8.71±3.05	7.13±1.56	8.19±3.41	7.86±2.97	0.051
2hrs PP (mmol/l)	11.98±3.99	9.27±1.79	11.62±4.21	10.49±3.72	0.049
HbA1c (%)	8.22±1.34	7.66±1.09	7.68±1.86	7.58±1.50	0.065
Serum cholesterol (mg/dl)	205.27±47.67	180.50±34.4	191.63±56.42	183.44±42.8	0.042
Serum triglyceride (mg/dl)	186.20±73.21	178.67±51.8	192.83±80.39	190.43±76.2	0.653
Serum HDL-C (mg/dl)	38.10±7.49	39.37±4.95	38.53±7.41	39.10±5.27	0.672
Serum LDL-C (mg/dl)	121.33±30.41	116.20±23.8	114.97±37.29	114.80±28.8	0.372

Data were presented as mean±SD. *p values were derived from independent sample t test.

Comparison of variables between Experimental group and Control group after 6 months of treatment. Among these changes only 2hrs PPBG and serum cholesterol were significant statistically (p<0.05) (Table II).

Table III Summary statistics of HCQ treatment effect on reduction of proteinuria by >30% from baseline to month 6 (n=30)

Group	Reduction of proteinuria		
	<30%	>30%	p value
Experimental group	15(50.0%)	15(50.0%)	<0.001
Control group	28(93.3%)	2(6.7%)	
EER	15/30	= 0.5	
CER	28/30	= 0.93	
RR	0.5/0.93	= 0.53	
ARR	0.93-0.5	= 0.43	
NNT	1/0.43	= 2	
		(95% CI=1.58 to 4.29)	

p values were derived from Chi-square test; EER: Experimental Event Rate, CER: Control Event Rate, RR: Relative Risk, ARR: Absolute Risk Reduction, NNT: Number Need to Treat, CI: Confidence Interval.

Reduction of proteinuria by >30% from baseline within 6months was taken as a significant outcome. Fifty percent of subjects of Experimental group had the favorable outcome in comparison to 6.7% in control group.The NNT (Number needed to treat) was 2, this means that about one in every 2 patients would benefit from the treatment (Table III).

Discussion

Both groups in the current study were similar at baseline in terms of biochemical parameter, age, gender, and presence of HTN length of DM. Characteristics of research population were comparable to those of the other studies carried out in this issue.[14,15]

Serum creatinine decreased statistically significantly in the experimental group from baseline to six months, while it increased in the control group. This difference was statistically significant (p <0.001) in the group comparison. Kushwaha et al.stated the experimental group's serum creatinine decreased from baseline to three months of therapy, whereas it was increased in control group. Siso et al. also described similar findings.[14,16]

The study results showed that after 6 months of follow up from baseline eGFR was found to be rising experimental group and decreased in the control group. In group comparison between experimental and control group which was highly significant (p<0.001). Kushwaha et al. and Lee et al. showed similar results where significant improvement of eGFR in HCQ treated group.[14,17]

Median uACR was reduced in experimental group and increased in control group from baseline to 6 months. The change of uACR in experimental group was significant compared to control group (p<0.001). Most recently, Kushwaha et al. done a non randomized controlled trial found that urinary ACR decreased in the HCQ group but continued to increase in the Non HCQ group.[1] Another studies also reported similar reduction of proteinuria in HCQ treated group.[9,18]

The present study found that serum total cholesterol was reduced significantly in HCQ treated group compared to non HCQ group (p=0.042). Regarding change of other lipid fraction (TG, LDL and HDL), it was not statistically significant at the end of the study (p>0.05). Gautom et al. found that, in the HCQ group (On combination of HCQ 100 mg twice daily and atorvastatin 20mg daily), HDL was increased and LDL and TG were declined significantly after 3 months of treatment and while the control group (On atorvastatin 20mg alone) observed decline of TGs and Cholesterol, but no improvement in HD and LDL after 3 months of treatment.[15]

Significant improvement in FBS, PPBG and HbA1c levels were found in experimental group. In contrast changes in HbA1c and FBG levels from baseline to 6 months follow-up were not significant statistically in Control group. Though PPBG reduction was significant (p <0.03) in Control group, the mean reduction was less prominent compared to experimental group (1.13 mmol/l versus 2.71 mmol/l). This effect of HCQ in reduction of glycemic parameters was supported by Jagnani et al. who reported that after 24 weeks of treatment, there were fall in fasting, postprandial blood sugar and HbA1c levels significantly in patients containing HCQ in comparison to Teneleglipti n.[19]

There were no meaningful differences between two groups in incidences of overall clinical adverse experiences. Moreover, there was no drug-related major adverse event that leads to discontinuation. This safety and tolerability profile of HCQ was also evident in the previous studies.[14,15,18,20,21]

There was no withdrawal or death in the present study. Both groups had lost to follow up, but they were not statistically significant.

These results clearly demonstrate the benefits and tolerability of HCQ in DN patients as an add on therapy with standard conventional treatment over 6 months which showed regression of nephropathy, glycemic and lipid advantages.

Limitation

The present study was conducted in a single center with small sample size in a short period of time. This was an open label clinical trial; both participant and researcher could be biased.

Conclusion

In conclusion, present randomized controlled trial conducted among patients with DN exhibit significant improvement of eGFR after 6 months treatment with HCQ as an add on therapy with other standard treatment. Moreover, there was significant reduction of serum creatinine and improvement of uACR among patients who received HCQ. In contrast, renal functions progressively declined in control group. These results are supportive of the renoprotective effects of HCQ in patients with diabetic nephropathy.

Recommendations

Based on the present study findings HCQ may be considering as an ideal add-on drug therapy in the treatment of DN patients receiving optimal conventional treatment. Larger triple blind multicenter studies with a longer follow-up are required to confirm the findings of the present study.

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Contribution of authors

MQI-Conception, acquisition of data, interpretation of data, drafting the article and final approval.

TKD-Acquisition of data, revision of content and final approval.

NN-Data analysis, critical revision of content and final approval.

SH-Critical revision of content, design, drafting and final approval.

RKS-Acquisition of data, revision of content and final approval.

NSA- Data analysis, drafting and final approval.

MNH-Conception, critical revision of content and final approval.

PKD-Conception, critical revision of content and final approval.

Disclosure

All the authors declared no conflict of interest.

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