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Original Research Article

Efficacy and Safety of Hydroxychloroquine as an Add-On Therapy in Indian Patients with Type 2 Diabetes Mellitus Inadequately Controlled With Two Oral Drug Combination and Basal Insulin: A 72 Week Observational Trial

Dr. Arjun Baidya[1], Dr. S. R. Pattanaik[2], Dr. Anand Shankar[3], Dr. Rishad Ahmed[4], Dr. Netrananda Dora[5], Dr. SaritaBehera[6]

[1]Associate Professor, Department of Endocrinology, NRS Medical College & Hospital, Kolkata
[2]Associate Professor, Department of Endocrinology, MKCG Medical College, Berhampur
[3]Shankar Diabetes Care Center, Patna
[4]Associate Professor, Dept. of Medicine, KPC Medical College & Hospital, Kolkata
[5]Diabetologist, Sambalpur
[6]Endocrinologist, Cuttack

Corresponding Author: Dr. S. R. Pattanaik

ABSTRACT

Aim: Patients who were inadequately controlled with multi drug along with exogenous insulin needs an additional drug to control their sugar level. It is always in need to opt for an economic anti diabetic drug which have long lasting efficacy with added benefits. The main objective of this study to evaluate long term efficacy and safety of Hydroxychloroquine as an add-on therapy in Indian patients with type 2 diabetes mellitus inadequately controlled with two oral drug combination and basal insulin.

Materials and methods: In this multicenter observational trial, 498 T2DM patients (male: 50.9%; age: 50.8 ± 8.3 years; time from T2DM diagnosis: 2.6 ± 1.2 years; baseline HbA1c: 8.1 ± 0.9%) with inadequate glycemic control on diet, exercise and combination of metformin and sulfonylurea were assigned to once daily treatment with hydroxychloroquine 400 mg. HbA1c (%) and, fasting plasma glucose levels (FPG) (mg/dL) and post prandial plasma glucose levels (PPG)(mg/dl) along with HsCRP and Serum creatinine was calculated at baseline, at 24 week, 48 weeks and 72 week.

Result: After addition of hydroxychloroquine 400 mg there was sustain reduction in glycemic parameters which was maintain even upto 72 weeks (p>0.001)(Table 2). In first 24th weeks HbA1c was reduced by 0.9±0.2, which was 0.4±0.5 at 48th week and 0.4± 0.1 at 72nd week. There were significant reduction in FPG and PPG after 72 week study which was -74±26 mg/dl (p> 0.001) and -145± 39 mg/dl (p> 0.001) respectively from baseline. It has been also found that there was frequent drastic reduction in insulin dose. There were 22% reduction by 24th week from baseline which was further reduced to 32% at 48 week and finally further 26% reduction of daily insulin dose at the end of 72 weeks. Apart of significant reduction in glycemic parameters, hydroxychloroquine also reduced inflammatory load and hs-CRP was reduced to 0.7 ± 0.3 mg/dl from 2.7 ± 0.8 mg/dl at the end of 72 weeks. Serum creatinine was unchanged over the entire treatment period. here was no report of withdrawals or treatment- emergent adverse events related to the study medications, during the treatment phase. Not a single eye has developed retinopathy of any grade.

Conclusion: The results confirmed the long term clinical benefit of a daily hydroxychloroquine 400 mg mg regimen in the Indian population and significantly reduce the dose of daily Insulin.

Keywords: Hydroxychloroquine, T2DM, Insulin, long-term efficacy.

INTRODUCTION

Diabetes together with cardiovascular disease ranking among 10th leading cause of mortality and consider as one of the largest global health emergencies of this country. [1,2] The current global statistics indicate that 8.8% of the adult population has diabetes with slightly higher rates in men (9.1%) compared to women (8.4%). [1] IDF has already been estimated that in 2045, the largest number of people with diabetes will be from India (134.3 million). [1] The explosion of diabetes in India also increases the predisposition for developing both micro and microvascular complications resulting in a huge burden due to morbidity and mortality leading to increase cost management.

Type 2 Diabetes Mellitus (T2DM)is a chronic condition that associated with significant comorbidities. Understanding the pathophysiological derangements involved in the occurrence of diabetes and related comorbidities inessential to plan out successful prevention and control strategies. An association has been noted between inflammatory biomarkers and the occurrence of type 2 diabetes and its comorbidities. [3] Inflammation is well known to play a central role in the pathogenesis of T2DM. [4] Anti-inflammatory drugs can potentially improve glycemic without causing hypoglycemia. Treatment interventions that address inflammation could have a role in the prevention of progressive decline in insulin secretion. [5] Excessive storage of nutrients in the adipose tissues gives way to an inflammatory response and IR. Intracellular lipid accumulations incite a pro inflammatory response by means of hypoxia and endoplasmic reticulum (ER) stress, which leads to apoptosis. [6] Several inflammatory targets have been identified that may affect metabolism. [7] Targeting these inflammatory molecules can have potential implications in the management of diabetes mellitus by possible improvements in various parameters associated with T2DM.

Hydroxychloroquine, being immunomodulatory and anti-inflammatory, [8] is widely used for the management of T2DM in India. Anti-diabetic effect of hydroxychloroquine may be due to inhibition of intracellular degradation of insulin as suggested by in vitro experiments. [9] Quatraro et al [10] demonstrated decreased insulin requirements in T2DM patients without altered C-peptide levels, suggesting unaltered secretion of insulin. Decreased IR has also been suggested to contribute to its anti diabetic effect. In one mechanistic study done by Wasko et al, [11] 20% improvement in insulin sensitivity and 45.4% improvement in beta cell functions observed. Surprisingly, the study also found 18.7% increase in adiponectin levels, which may be responsible for its insulin-insulin-sensitising effect. In a double blind, randomised comparison of hydroxychloroquine with pioglitazone by Pareek et al, [12] shoed that control on glycemic parameters by hydroxychloroquine was similar to that of pioglitazone in the patients unresponsive to metformin and sulfonylurea combination along with a significant improvements in lipid profile.

The addition of hydroxychloroquine to insulin therapy caused a significant decrease in the glucose profile and daily insulin dose (30% decrease). [10] In few observational study. Daily insulin dose was also decreased significantly over 24 weeks of time from baseline in a large proportion of patients. [13- 15] Till now there were no trial to evaluate long term efficacy and safety with hydroxychloroquine and its ability to reduce daily insulin dose. The main objective of this study to evaluate long term efficacy and safety of Hydroxychloroquine as an add-on therapy in Indian patients with type 2 diabetes mellitus inadequately controlled with two oral drug combination and basal insulin.

MATERIALS AND METHODS

In this multicenter observational trial, 498 T2DM patients (male: 50.9%; age:

50.8±8.3 years; time from T2DM diagnosis: 2.6±1.2 years; baseline HbA1c: 8.1±0.9%) with inadequate glycemic control on diet, exercise and combination of metformin and sulfonylurea were assigned to once daily treatment with hydroxychloroquine 400 mg. HbA1c (%) and, fasting plasma glucose levels (FPG) (mg/dL) and post prandial plasma glucose levels (PPG)(mg/dl) along with HsCRP, daily dose of Insulin and serum creatinine was calculated at baseline, at 24 week, 48 weeks and 72 week.

T2DM patients whose HbA1c was in between 7.0 % to 9 % and with body weight ≥60 kg and also able to understand and willing to fully comply with study procedures and restrictions, included in the study. Ophthalmic screening was done with ophthalmologist to exclude patients at baseline who had any type of retinopathy, maculopathy or retinal abnormalities. Patients who had and past history of CV event or CKD was excluded from the study. Patient with known history of diabetic ketoacidosis, glucose-6- phosphate dehydrogenase deficiency, known allergy to the substance, pregnancy and breastfeeding were also excluded from the study.

Primary objective of the trial was to evaluate the changes in glycemic parameters (HbA1c, FPG and PPG) after 72 weeks from baseline and the secondary objective was to calculate total daily dose reduction of insulin, reduction in inflammatory markers like HsCRP, no of hypoglycaemic events and change of serum creatinine level.

Monitoring for adverse experiences, physical examinations, vital signs, body weight, ECG, laboratory measurements comprising routine haematology, serum chemistry and urinalysis were performed in a NABL accredited pathology laboratory attached to across study centers. Adverse experiences of special interest included hypoglycemia.

This study was conducted in accordance with the good clinical practice guidelines and with the Helsinki Declaration principles. Individual ethical committee approval was obtained prior to the trial from each centers. Also prior to conduct of study related procedure/investigation, a voluntary written informed consent was taken from the patient /legally acceptable representative.

For the demographic details, analysis was done descriptively. Quantitative data of FPG, PPG and HbA1c from baseline to 24 weeks (6 months), 48 weeks (12 month) and 72 weeks (18 month) after combination anti-diabetic regimen was analysed by two-tailed paired t-test for data. Statistical software (GraphPad Prism5; version 5.01) was used for analysis. Statistical tests were considered significant if P-value was <0.05 at confidence interval of 95%.

RESULT

498 patients were analysed to evaluated long term efficacy of the trial. Baseline characteristics of the trial were demonstrated in table 1. Among 498 patients 50.9% were male and average mean age was 50.8 ± 8.3 years. Baseline HbA1c was found to be 8.1 ± 0.9% with 2.6 ± 1.2 years as mean duration of diabetes. Baseline hs-CRP was found to be 2.7 ± 0.8 and serum creatinine (S. Cr.) was 0.67 ± 0.2.

Table 1:Baseline characteristics of study participants.

Variables	N= 498
Age (Years)	50.8 ± 8.3
Male	253 (50.8%)
Diabetes Duration (Years)	2.6 ± 1.2
BMI (Kg/m2)	26.30 ± 4.15
Weight (Kg)	67.81 ± 3.79
Daily Insulin Dose (IU/D)	49 ± 12
HbA1c (%)	8.1 ± 0.9
FPG (mg/dl)	179 ± 18
PPG (mg/dl)	294 ± 38
HsCRP (mg/dl)	2.7 ± 0.8
S. Cr. (mg/dl)	0.67 ± 0.2

After addition of hydroxy-chloroquine 400 mg there was sustain reduction in glycemic parameters which was maintain even upto 72 weeks (p>0.001)(Table 2). In first 24th weeks HbA1c was reduced by 0.9±0.2, which was 0.4±0.5 at 48th week and 0.4±0.1 at 72nd week. There were significant reduction in FPG and PPG after 72 week study which

was -74±26 mg/dl (p> 0.001) and -145± 39 mg/dl (p> 0.001) respectively from baseline.

It has been also found that there was frequent drastic reduction in insulin dose. There were 22% reduction by 24th week from baseline which was further reduced to 32% at 48 week and finally further 26% reduction of daily insulin dose at the end of 72 weeks.

Table 2: Change from baseline to 72 week study end point with Hydroxychloroquine 400mg

Characteristic	Hydroxychloroquine 400 mg (N=498)											
	Baseline	24 weeks	Δ from baseline	P value	48 Weeks	Δ from 24th week	P value	72 weeks	Δ from 48th week	P value	Δ from baseline	P value compare to baseline
Daily Insulin Dose (IU/D)	49 ± 12	38 ± 9	11±7	> 0.05	26 ± 10	12±4	> 0.01	19 ± 7	7±4	> 0.01	30±8	> 0.001
HbA1c (%)	8.1 ± 0.9	7.2 ± 0.6	0.9±0.2	> 0.05	6.8 ± 0.6	0.4±0.5	> 0.01	6.4 ± 0.3	0.4±0.1	> 0.01	1.7±0.5	> 0.001
FPG (mg/dl)	179 ± 18	134 ± 21	45± 12	> 0.05	118 ± 9	16±6	> 0.01	105 ± 8	13±7	> 0.01	74±26	> 0.001
PPG (mg/dl)	294 ± 38	214 ± 24	80±14	> 0.05	173 ± 31	41±11	> 0.01	149 ± 19	24±8	> 0.01	145± 39	> 0.001
HsCRP (mg/dl)	2.7 ± 0.8	1.6 ± 0.3	1.1± 0.1	> 0.05	1 ± 0.4	0.6±0.1	> 0.01	0.7 ± 0.3	0.3±0.1	> 0.01	2±0.2	> 0.001
S. Cr. (mg/dl)	0.67 ± 0.2	0.68 ± 0.1	+0.01±0.01	0.432	0.66 ± 0.2	0.02±0.01	0.821	0.66 ± 0.1	0.0±0.01	0.931	0.01±0.01	0.739

Apart of significant reduction in glycemic parameters, hydroxychloroquine also reduced inflammatory load and hs-CRP was reduced to 0.7 ± 0.3 mg/dl from 2.7 ± 0.8 mg/dl at the end of 72 weeks. Serum creatinine was unchanged over the entire treatment period. Not a single eye has developed retinopathy of any grade.

Table 3: Adverse events reported during the treatment period.

Adverse event	Hydroxychloroquine 400 mg (N=498)
Discontinuation for adverse event	0
Severe Symtomatic Hypoglycemia	2
Moderate Symptomatic Hypoglycemia	32
Mild Symptomatic Hypoglycemia	52
Weight increased	0
Nausea	1
Dyslipidemia	4
Gasto intestinal adverse events	12
Any grade of Diabetic retinopathy	0
Number of patients	82

Without any serious adverse effects all patients tolerated the drug hydroxychloroquine 400 mg once daily well. There was no report of withdrawals or treatment- emergent adverse events related to the study medications, during the treatment phase. Not a single eye has developed retinopathy of any grade (Table 3). There were no emergency medication required to handle any adverse event include severe symptomatic hypoglycemia. Hypoglycemia with hydroxychloroquine is the main reason to taper down the dose of basal insulin. It has been also observed when patients detected or complain of hypoglycemia, step wise dose reduction of insulin dares the situation.

Adverse event represented by preferred term. One patient may have reported more than one adverse event.

DISCUSSION

Efficacy of hydroxychloroquine in the treatment of T2DM has gradually become evident. Initial observational retrospective cohort studies in RA patients demonstrated significant reduction in the risk of incident diabetes. [16] The findings from this epidemiological study was considered hypothesis-generating and various other observational cohort studies also suggested the potential benefit of hydroxychloroquine in attenuating the risk of diabetes in patients with RA. [17, 18] Our trial was one of the first of its kind initial observational trial which confirms the longterm safety oh hydroxychloroquine.

Emami et al, [19] have shown glucose and insulin homeostasis with hydroxychloroquine in their experimental study and it has also appears in this study that hydroxychloroquine sustain higher insulin levels and hence has therapeutic potential in the treatment of patients who have reduced beta cell function.

Hydroxychloroquine also increased insulin binding to its receptor and altered hepatic insulin metabolism, thereby potentiating insulin action. [20] This is the main reason that even in this trial there were significant decreases in insulin dose. It has been also found that there was frequent drastic reduction in insulin dose. There were 22% reduction by 24th week from baseline which was further reduced to 32% at 48 week and finally further 26% reduction of daily insulin dose at the end of 72 weeks. This results was in line with other trials which also confirms daily insulin dose reduction in tune of 28 -30% over 24 weeks of time.

West of Scotland Coronary Prevention Study (WOSCOPS) [21] added to the accumulation evidence implicating inflammation as a potential pathway in the pathogenesis of T2DM. It was demonstrated that CRP predicts the development of T2DM independently of established risk factors including fasting plasma triglyceride, body mass index (BMI) and glucose. In addition, it was seen that subjects in the top quintile of CRP (>4.18 mg/L) had a more than three times increased risk of developing diabetes compared with those in the lowest quintile (0.66 mg/L) after adjusting for the other variables. [22] This data strongly added to the concept of low grade inflammation having a key role in the pathogenesis of T2DM. Even n this observational trial it has been observed the reduction in inflammatory load helps to achieve a significant glycemic control and which continues for a long term.

Hydroxychloroquine has been shown to exert Nephro-protective effect by significantly reducing the risk and progression of lupus nephritis in patients with SLE which is another chronic inflammatory disorder. [23, 24] In our trial there were no alterations of serum creatinine throughout the study. Even in two pre-clinical studies which have been conducted in India academic centers to evaluate there of hydroxychloroquine in diabetic nephropathy, demonstrated that hydroxychloroquine and its combination with renin-angiotensin-aldosterone system (RAAS) blockers resulted in improving in biochemical and renal oxidative stress parameters like serum creatinine and glutathione. [25, 26]

Considering the need of ophthalmic monitoring in patients on long-term, therapy with hydroxychloroquine, in this trial at baseline patients was screened to rule to any grade of diabetic retinopathy or maculopathy. In our trial hydroxychloroquine dose was maintained as per AAP2016 [27] guideline and at the end of 72 weeks treatment no patients had developed any grade of retinopathy.

CONCLUSION

The results confirmed the long term clinical benefit of a daily hydroxychloroquine 400 mg mg regimen in the Indian population and significantly reduce the dose of daily Insulin. Although several agents are available for the management of patients with diabetes, hydroxychloroquine has generated significant attention in recent past and this trial even expand the horizon and one of the first of its kind by confirming the long term efficacy and safety for treating T2DM.

Limitations

The sample size for this study was small. However, based on the encouraging results of this study, longer duration studies in larger population can be conducted to further confirm these findings.

Disclosure

The authors report no conflicts of interest in this work. No funding sources.

Contributors

All authors had full access to all data, and take responsibility for the integrity of the data and accuracy of analyses. All authors actively participated in the preparation of the manuscript and provided critical review at each step.

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