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Research Article
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Effect of Hydroxychloroquine on Type 2 Diabetes Mellitus Unresponsive to More Than Two Oral Antidiabetic Agents

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Abstract

Background and aims: The aims of the present study were to evaluate the effectiveness of Hydroxychloroquine as an add-on therapy to metformin and Sulfonylurea (SU) in reducing glycosylated hemoglobin (HbA1c) to achieve therapeutic goals.

Methods: In this open-labelled comparative observational study, two groups of 100 uncontrolled Type 2 Diabetes Mellitus (T2DM) patients in each were studied for 24 Weeks (6 months). Both the groups were divided into patients who were on triple drug combinations. One group receiving Metformin,Glimepiride and Teneleglitpin and the other group received Metformin,Glimepiride and Hydroxychloroquine. In each group fasting blood sugar and as postprandial blood sugar were tested at the start of the study and at 4 weeks intervals. HbA1c was tested at the beginning of study, at 12 Weeks (3 months) and at the end of 24 weeks (6 months).

Results: After 24 weeks of treatment, there was significant fall in fasting, as well as postprandial blood sugar and HbA1c levels in patients containing Hydroxychloroquinine in comparison to Teneleglitpin.

Conclusions: Hydroxychloroquine significantly improves glycaemic control in patients with T2DM when prescribed as an add-on therapy in addition to two other commonly prescribed antidiabetic drugs such as Glimipirde and metformin combination, and even its efficacy to reduce blood sugar is compairable to newer generation drugs like Teneligliptin. Hydroxychloroquine may be considering as an ideal add-on third drug therapy in the treatment of uncontrolled T2 DM patients.

Keywords: Glycemic control; Hydroxychloroquine; Type 2 diabetes mellitus

Introduction

Diabetes mellitus is the fourth leading cause of death worldwide, following cancer, cerebrovascular disease, and heart disease. It is triggered by hyperglycemia and other metabolic disorders. In India type 2 Diabetes consider as a major health problem and no of uncontrolled patients are increasing day by day. As per 2015 International Diabetes Federation (IDF) report India is 2nd largest diabetic population which is second to china (109.6 million) and having almost 69.2 million diabetic patients [1].

Diet and lifestyle modifications are of primary importance when we treat any type 2 diabetic patients. This is even advised by all leading guideline [2]. Generally the first drug we used in newly diagnosed T2DM is metformin, if further blood sugar is not controlled we generally add a second drug which is mostly second generation sulfonylurea like Glimepiride. A third line drug is introduced when blood sugar is further not controlled. Most patients initially respond to sulfonylurea and/or metformin, and later these agents lose their effectiveness with time [3,4]. Combination therapy using agents with complementary but different mechanisms of action that address different pathophysiologic defects of type 2 diabetes may improve glycemic control to a greater extent than monotherapy.

There are several options of third line drug to treat uncontrolled T2DM. Teneligliptin which inhibits DPP-4 and thus increase incretion hormones like glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) in the intestine. Teneligliptin was introduced in India in May 2015. It has gained popularity and is already widely prescribed in type 2 diabetes mellitus (T2DM). However, several questions remain, on the efficacy and "in particular" safety of teneligliptin. Safety point of view, prolongation of QTc is a unique issue with teneligliptin [5].

Inflammation is considered to play a crucial intermediary role in pathogenesis of diabetes and number of co-existing disease. Hydroxychloroquine, a long-standing safe and inexpensive treatment for autoimmune disorders, may theoretically improve glucose tolerance and prevent diabetes. Hydroxychloroquine, inhibits insulin degradation and improve insulin sensitivity. A few randomized controlled trials showed that HCQ lowers HbA1c and LDL cholesterol

levels in patients with type 2 diabetes [6]. Furthermore, in a, prospective, randomized, placebo, double-blind 6-month trial, the addition of Hydroxychloroquine to either insulin or glibenclamide in the treatment of refractory noninsulin-dependent diabetes for 6 months resulted in a significant decrease in HbA1C by 3.3% compared with placebo as well as a reduction in insulin dose by 30% in the insulin-treated group [7].

The glycemic efficacy was assessed by analysing the mean change in values of glycosylated hemoglobin (HbA1c), Fasting Blood Sugar (FBS), and postprandial blood sugar (PPBS) from baseline following combination of Telegliptin based therapy and compared with Hydroxychloroquine based combination therapy.

Methods

This comparative observational study was conducted in a tertiary care clinics of Ranchi, Jharkhand and Kolkata, West Bengal, India from January 2017 to August 2017. Total duration of study was 24 weeks.

Information for this comparative observational study, which include antidiabetic medications, HbA1c/FBS/PPBS status at the beginning and periodic interval after adding add-on therapy, demographic data was collected by using a predesigned structured proforma.

At every 4 weeks (3 months) intervals Fasting Blood Sugar (FBS), and postprandial blood sugar (PPBS) were tested .HbA1c status was tested at beginning and 12 weeks (3 months) interval. I each patient's body weight, gender & marital status, age, BMI, concomitant disease like neurological disorder, systemic hypertension, hepatic or renal disorder and bronchial asthma were recorded. We had taken the past history of medication for T2DM of each patients. We have carefully noticed any type of drug reaction.

Inclusion criteria

- Subjects who were suffering from T2DM and already on antidiabetic drug combination (SU and Metformin).
- Body weight: ≥ 60 kg
- Subject's age more than 18 years of either sex
- Willing to give informed consent for the study.

Exclusion criteria

- Subjects not agreeing to participate
- Subjects with a history of retinopathy
- Subjects with uncorrected visual acuity <20/100, abnormal visual fields, difficulty examining the optic disc, or evidence of retinal pigment, epithelial abnormalities and history or risk of macular edema.
- History or risk of psoriasis, rash, scaling or scaling eczema, porphyria.
- History of recent cardiovascular events, active gastrointestinal or haematological disorders
- History of diabetic ketoacidosis & Subjects with G6PD deficiency
- Pregnant or lactating women

Analysis was done descriptively for the demographic details. Quantitative data of FPG, PPG and HbA1c from baseline to 12 weeks (3 months) after combination antidiabetic regimen was analyzed 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%.

Results

In this present study we have analyzed a data of 200 patients. Baseline population and clinical characteristics of the study participants was shown in Table 1 and 2. 57.84 ± 10.32 years was the mean age of patients. 76% were males and 24% were females out of the entire patient population. Almost 64% (n=200) of patients had comorbid conditions, and rheumatoid arthritis (26%), Dyslipidaemia (23.5%) and hypertension (19.5%) were the most common one (Table 2).

Patients belongs to group (2) Figures 1-3, getting Hydroxychloroquine along with metformin (200 mg) and glimepiride (2mg), show significant reduction (P-value 0.0001) of FBS (-46 ± 25), PPBS (-78 ± 37) and HbA1c (-1.8 ± 1.1) is clearly evident From Table 3 and 4.

Groups [A/B]	Treatment Allotted	No. of the patients in each group
Group [1]	Metformin (2000 mg), Glimepiride (2 mg), Teneligliptin (20 mg)	100
Group [2]	Metformin (2000 mg), Glimepiride (2 mg), Hydroxychloroquine (400 mg)	100

Table 1: Two groups (N==200 at baseline) of patients and their medication doses under study.

Patients characteristics		Group 1 Teneligliptin Group (N=100)		Group 2 Hydroxychloroquine Group (N=100)		Total (N=200)		p Value
		Number of patients, n (%)	Mean (SD)	Number of patients, n (%)	Mean (SD)	Number of patients, n (%)	Mean (SD)	
Gender	Male	74 (74%)	74 (56.3)	78 (78%)	78 (57.9)	152 (76%)	123 (56.7)	0.433
	Female	26 (26%)	26(23.8)	22 (22%)	22 (24.12)	48 (24%)	48 (23.9)	
Age	≤ 60 years	28 (28%)	58.84(10.32)	32 (32%)	58.84(10.32)	60 (30%)	58.84(10.32)	0.623
	>60 years	72 (72%)		68 (68%)		140 (70%)		

Duration of diabetes (years)	≥ 4 Years	74 (74%)	4.53 (3.80)	80 (80%)	4.82 (3.64)	154 (77%)	4.63 (3.71)	0.649
	≤ 4 Years	26 (26%)		20 (20%)		46 (23%)		
Baseline HbA1c (%)	<7.5	24 (24%)	9.2 (1.2)	15 (15%)	9.3 (1.1)	39 (19.5%)	9.3 (1.1)	0.739
	≥ 7.5- ≤ 9	32 (32%)		28 (28%)		60 (30%)		
	>9	44 (44%)		57 (57%)		101 (50.5%)		
Baseline FPG (mg/dL)	≤ 126	10 (10%)	171.20 (41.47)	10 (10%)	173.20 (41.87)	20 (10%)	172.20 (41.67)	0.319
	>126	90 (90%)		90 (90%)		180 (90%)		
Baseline PPG (mg/dL)	≤ 200	18 (18%)	266.68 (61.40)	19 (19%)	268.68 (61.57)	37 (18.5%)	267.68 (61.50)	0.849
	>200	82 (82%)		81 (81%)		163 (81.5%)		
Medication for other co-morbid conditions	Anti-hypertensive (s)	23(23%)		16 (16%)		39 (19.5%)		
	Statins	23 (23%)	24 (24%)	47 (23.5%)				
	Antiplatelet drugs	12 (12%)	14 (14%)	26 (12.5%)				
	Anti-Rheumatic Drug	12 (12%)	40 (40%)	52 (26%)				

Table 2: Populations (n=200) and clinical characteristics of the study participants at baseline.

Outcome Glycemic Parameters	Group 1 Teneligliptin Group (N=100)	Group 2 Hydroxychloroquine Group (N=100)	p Value
HbA1c, %			
Baseline	9.2 (1.2)	9.3 (1.1)	0.745
Week 12	8.1 (1.1)	8.00 (1.1)	0.074
Change from baseline at Week 12	1.1 (1.1)	1.3(1.1)	0.394
p Value	<0.0001	<0.0001	
Week 24	7.6 (1.1)	7.5 (1.1)	0.909
Change from baseline at Week 24	(-) 1.6 (1.98 - .87)	(-)1.8 (2.05 - 0.85)	0.936
p Value	<0.0001	<0.0001	
FPG (mg/dL)			
Baseline	171.20 (41.47)	173.20 (41.87)	0.319
Week 12	136.28 (43.21)	130.29 (39.34)	
Change from baseline at Week 12	38 ± 26	43 ± 28	0.729
p Value	<0.0001	<0.0001	0.769
Week 24	132.29	128.5	0.529
Change from baseline at Week 24	40 ± 31	46 ± 25	0.628
p Value	<0.0001	0.005	
PPG (mg/dL)			
Baseline	266.68 (61.40)	268.68 (61.57)	0.849
Week 12	197.58 (71.21)	194.69 (71.38)	0.423

Change from baseline at Week 12	71 ± 35	73 ± 31	0.413
p Value	0.008	0.046	
Week 24	194.68 (69.78)	190.68 (71.21)	0.419
Change from baseline at Week 24	72 ± 32	78 ± 37	0.423
p Value	0.002	<0.0001	

Values presented as mean (SD), and compared using two sample t test.

Least square mean change from baseline (95% CI) adjusted to its baseline value.

Comparison with baseline using paired t test.

HbA1c - glycosylated hemoglobin; FBG - fasting blood glucose; PPG - postprandial glucose.

The above analysis was performed on the modified intention to treat population which comprised patients who had completed the study upto at least Week 12 without any protocol violation.

Table 3: Mean reduction in glycemic parameters compared to baseline (after 3 & 6 month).

Category	FPG (mg/dL)	PPG (mg/dL)	HbA1c (%)	% of patients achieved, HbA1c <7%
Teneli + Met + Glmi (n=100)	40 ± 31	72 ± 32	1.6 ± 1.1	42
HCQ + Met + Glmi (n=100)	46 ± 25	78 ± 37	1.8 ± 1.1	61

Note: Values are presented as mean ± standard deviation otherwise mentioned. P-value <0.0001 for all glycemic parameters in all subgroups

Table 4: Reduction of FBS, PPBS and HbA1c after b6 months of therapy.

It is evident from above column chart that after 24 weeks (6 months) of therapy that the reduction of FBS, PPBS and HbA1c was greater in Group 2, containing Hydroxychloroquine compared to group 1 containing Teneligliptin.

At 24th week eye scanning was done. Eye check-up done to evaluate corrective lenses, it has been found that in all patients (n=200) pupils are equal and reactive to light and accommodation, Fundi-clear, no arteriolovenous nicking, no retinopathy.

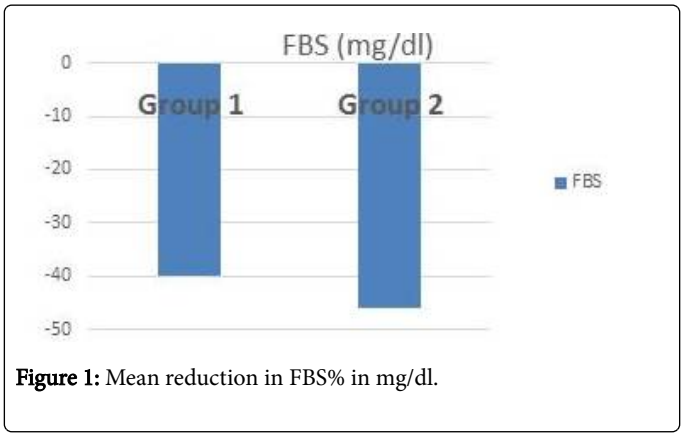

Figure 1: Mean reduction in FBS% in mg/dl.

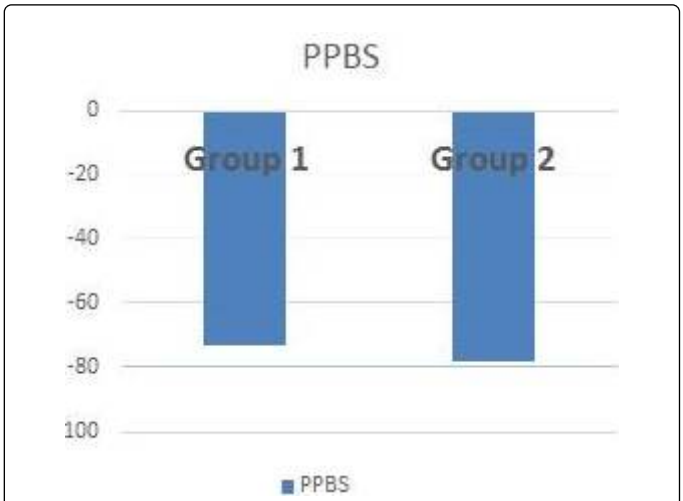

Figure 2: Mean reduction in PPBS% in mg/dl.

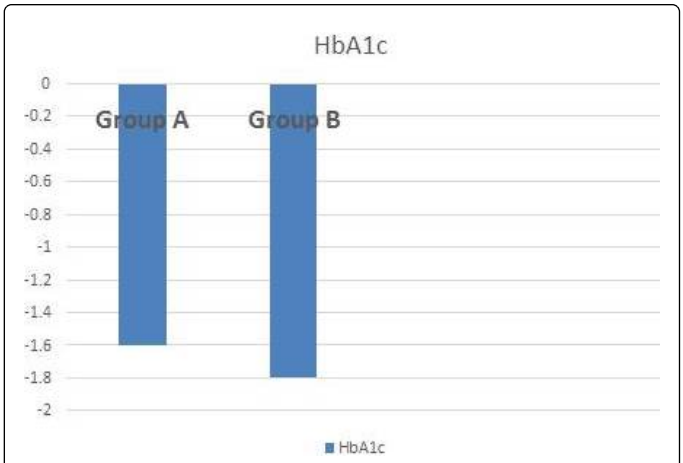

Figure 3: Mean reduction in HbA1c%.

Discussion

Diabetic patients require multiple drugs to control blood sugar levels and to minimize long-term complications which are associated with diabetes. The association between hyperglycemia, inflammation, and vascular complications in diabetes is now well established. Since metabolic dysregulation itself induces inflammation, effective antidiabetes treatments may alleviate inflammation by virtue of improving the metabolic state [8]. Chronic inflammation plays an important role in the development and progression of diabetes and its complications. Better understanding of the inflammatory basis for diabetes may provide improved modalities for diabetes prevention and treatment [9]. Hydroxychloroquine has a well-established safety profile and its multifaceted effects are well documented too. It slows breakdown of the internalized insulin-receptor complex [10] and a study in obese, non-diabetic individuals reported a significant increase in insulin sensitivity index and trends toward reduced insulin resistance and insulin secretion [11]. A previous epidemiological study 10 has reported 77% reduction in development of diabetes in rheumatoid arthritis patients with Hydroxychloroquine use for >4 years compared to those who never used Hydroxychloroquine.

Hydroxychloroquine is usually given 400 mg once daily after dinner dose. Not a single case of sever hypoglycemia associated to addition of Hydroxychloroquine, any type of edema and sever weight gain was reported during study period. No significant drug interactions are there and usually well tolerated. No progression of diabetic retinopathy has reported in both the groups.

In this observational trial patients are on optimum dose of metformin and glimepiride indicating that patients had had the disease for a significant duration. Robust glycemic benefit in such patients with diabetes of significant duration and poor glycemic status reemphasizes that Hydroxychloroquine is a potent/efficacious drug for treatment of patients with type 2 diabetes. This finding also supports, and is in line with, the findings of the UKPDS study which suggested that polypharmacy is required to attain glycemic targets in patients with type 2 diabetes [12].

Hydroxychloroquine is considered as the safest disease modifying anti-rheumatic drug. The major safety concern with long-term Hydroxychloroquine use is retinopathy, the incidence of which according to the American Academy of Ophthalmology can be minimized by keeping the daily dose 56.5 mg/kg/day. The need of annual screening is now reduced to baseline screening and subsequent screening only after 5 years of Hydroxychloroquine use [13]. The largest series of rheumatologic patients showed only one case of clear toxicity among 1207 users [14]. Thus, Hydroxychloroquine can be safely used for at least 5 years in patients who are uncontrolled on oral combination therapy and are reluctant to use insulin.

Our study included comparatively severe diabetes patients as mean HbA1c at baseline was 9.3% and mean duration of diabetes was 4.6 years. The majority of patients (>63%) had one or more comorbid condition like hypertension and dyslipidemia. This high prevalence of comorbid conditions in this study is in accordance with previously reported studies done in India [15].

The reduction in glycemic parameters strongly correlated with baseline glycemic values, that is, higher the HbA1c at baseline; higher was the reduction at the end of 6 months. Reduction in FPG and PPG was observed relative to corresponding baseline values. The majority of patients (64%) had one or more comorbid condition like hypertension, dyslipedemia and rheumatoid arthritis. Patients with co-morbid conditions were on different anti-hypertensives, statins, anti-platelet monotherapy or combination therapy.

Considering the multifaceted effects of hydroxychloroquine, it could slow down the progression from the prediabetes stage to diabetes and can also improve the cardiovascular risk profile in diabetes patients with its favorable actions on blood glucose, lipid profile and anti-thrombotic properties, making it an attractive therapeutic choice for the treatment of T2DM patients. In a study conducted by Quatraro et al. [7], use of Hydroxychloroquine along with insulin led to a reduction in insulin dose by an average of 30%. However, the sample size for this study was small. Based on the encouraging results of our proof-of-concept study, there is further scope for evaluating role of Hydroxychloroquine in patients receiving insulin to assess whether dose of insulin is reduced when Hydroxychloroquine is used as an add-on therapy. Besides, further evaluation in clinical trials are warranted with a large number of patients and longer study duration for thorough ophthalmologic monitoring and cardiovascular outcomes assessments.

This comparative observational study has certain limitation, because of the observational and retrospective deign of the study, the possibility of selection bias cannot be ruled out. Information related to diet and lifestyle modification and information regarding dosing pattern of concomitant medication was not analysed. Data were collected only for duration of 6 months, so there are limitations in commenting on durability of the treatment. Long-term studies to address the shortcomings of the present study are warranted.

Conclusion

Hydroxychloroquine 400 mg once a day is an effective add-on for getting good glycemic control when appropriately used in type 2 diabetes mellitus patients who are poorly controlled on other oral agents.

Disclosure

The authors report no conflicts of interest in this work. No funding sources. The study was approved by ethical committee of Jharkhand IACC.

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