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Original article
Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with pioglitazone

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Abstract

Objective:
To compare efficacy and safety of hydroxychloroquine with pioglitazone in type 2 diabetes mellitus (T2DM).

Research design and methods:
This double-blind study randomized 267 uncontrolled type 2 diabetes patients (HbA1c $\geq$7.5% and $\leq$11.5%), post 3 months' treatment with glimepiride/gliclazide and metformin, to additionally receive hydroxychloroquine 400 mg/day ($n=135$) or pioglitazone 15 mg/day ($n=132$) for 24 weeks. Efficacy was assessed by changes in HbA1c, fasting (FBG) and post-prandial (PPG) blood glucose at Week 12 and Week 24.

Results:
At Week 12 and Week 24, HbA1c, FBG and PPG significantly reduced from baseline in both groups. Mean reduction in glycemic parameters at Week 12 (HbA1c: −0.56% vs −0.72%, $p=0.394$; FBG: −0.99 mmol/L vs −1.05 mmol/L, $p=0.878$; PPG: −1.93 mmol/L vs −1.52 mmol/L, $p=0.423$) and Week 24 (HbA1c: −0.87% vs −0.90%, $p=0.909$; FBG: −0.79 mmol/L vs −1.02 mmol/L, $p=0.648$; PPG: −1.77 mmol/L vs −1.36 mmol/L, $p=0.415$) was not significantly different between the hydroxychloroquine and pioglitazone groups. Change in total cholesterol (TC) and LDL-C was significant in favor of hydroxychloroquine (TC: −0.37 mmol/L vs 0.03 mmol/L, $p=0.002$; LDL-C: −0.23 mmol/L vs 0.09 mmol/L, $p=0.003$). Triglycerides significantly reduced in both groups at Week 24. Mean HDL-C remained unchanged. Study treatments were well tolerated.

Conclusion:
With favorable effects on glycemic parameters and lipids, hydroxychloroquine may emerge as well tolerated therapeutic option for T2DM.

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

Trial registration details:
Clinical Trial Registry–India URL: http://ctri.nic.in, Registration Number: CTRI/2009/091/001036.

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Introduction

Currently available anti-diabetic drugs are used alone or in combination to improve glucose homeostasis via different modes of action. Most patients initially respond to sulfonylurea and/or metformin, and later these agents lose their effectiveness with time[1,2]. For patients uncontrolled on two-drug combination therapy, the option left is either addition of third oral drug or insulin. However, high cost and poor compliance limits use of insulin. The new treatment options like gliptins and SGLT2 inhibitors are costly considering they are still under patent. Thus, many diabetic patients in low and middle income countries, where the incidence of diabetes is increasing rapidly, may not be able to afford such costly medicines considering the longer duration of treatment required.

The thiazolidinedione class of drugs is associated with adverse effects like fluid retention and weight gain[3] that may result in or exacerbate edema and congestive heart failure[4]. Recent study has also shown that use of pioglitazone is associated with an increased risk of bladder cancer in T2DM patients[5]. Thus there is a need for a safe and inexpensive treatment option for the treatment of diabetes mellitus.

Hydroxychloroquine, a long-standing safe and inexpensive treatment for autoimmune disorders, may theoretically improve glucose tolerance and prevent diabetes. The mechanisms of hypoglycemia with hydroxychloroquine are inferred from studies of chloroquine, a structurally similar anti-malarial, which have been shown to alter insulin metabolism in humans by both increasing insulin secretion and inhibiting its clearance, leading to hypoglycemia[6]. Animal data have shown increased insulin levels in hydroxychloroquine treated diabetic rats[7] and have also been shown to inhibit insulin metabolism in rat liver cells[8]. It has been shown to reduce HbA1c in patients with T2DM who have suboptimal glucose control[9]. Hydroxychloroquine has also been shown to reduce serum cholesterol levels in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients[10].

Hydroxychloroquine showed improved glycemic control in a cross-sectional study of cardiovascular diseases risk factors in women with SLE or RA[11] and in sulfonylurea refractory patients[12]. An observational study of 4905 RA patients[6] showed a reduced risk of developing diabetes in patients with hydroxychloroquine use compared to those who never used hydroxychloroquine.

Inflammation is considered to play a crucial intermediary role in pathogenesis of diabetes and number of co-existing disease. Interlukin-6 and C-reactive protein are two sensitive physiological markers of sub-clinical inflammation, associated with hyperglycemia, insulin resistance, and overt T2DM[13]. A recent study in SLE and RA patients has demonstrated that hydroxychloroquine inhibits production of interlukin-6 and other inflammatory markers[14]. Another long-term randomized trial on hydroxychloroquine in RA patients has demonstrated favorable effects of hydroxychloroquine on C-reactive protein showing a reduction of 20 mg/L from its initial value post 5 years of hydroxychloroquine use[15].

Despite this evidence, no study has been conducted on hydroxychloroquine in comparison with another anti-diabetic agent in T2DM. Our study aimed at exploring the comparative anti-hyperglycemic potential of hydroxychloroquine with pioglitazone as a third-line treatment in T2DM patients uncontrolled on a combination of gliclazide or glimepiride with metformin. Pioglitazone was selected as a comparator because it is the most commonly used third-line drug in the management of T2DM.

The comparative efficacy evaluation was based on change in glycemic parameters (HbA1c and blood glucose), lipid profile and body weight.

Patients and methods

Study design

This double-blind, double-dummy, randomized, comparative, multicenter study was conducted at 15 centers across India between December 2009 and July 2013. The study was conducted in accordance with the ethical principles of Declaration of Helsinki. The study was approved by respective ethics committee at all centers. All patients provided their written consent before participation. The study involved optional pre-run-in period, compulsory 3 months' run-in period, and 6 months' treatment period. Type 2 diabetes patients uncontrolled on two-drug combination therapy with HbA1c between ≥7.5% and ≤13.0%, FBG >7.22 mmol/L, and PPG >10 mmol/L, satisfying eligibility criteria and receiving metformin at least 1000 mg/day in combination with either glimepiride at least 4 mg/day or gliclazide at least 160 mg/day, entered the run-in period. Patients with HbA1c between ≥7.5% and ≤13.0%, FBG >7.22 mmol/L, and PPG >10 mmol/L, satisfying eligibility criteria and receiving metformin <1000 mg/day in combination with glimepiride <4 mg/day or gliclazide <160 mg/day entered the pre-run-in period wherein dose of glimepiride was increased by 2 mg/day or dose of gliclazide was increased by 80 mg/day or dose of metformin was escalated by 500 mg/day every 2 weeks as per investigator's assessment. The dose of only one drug was escalated at a time. Once patients reached metformin at least 1000 mg/day in combination with either glimepiride at least 4 mg/day or gliclazide at least 160 mg/day, they were maintained at the same dose during 3 months' run-in period. Post 3 months run-in period, patients with HbA1c between ≥7.5% and ≤11.5%, FBG >7.22 mmol/L and PPG >10 mmol/L, satisfying eligibility criteria were randomized to receive either hydroxychloroquine 400 mg/day or pioglitazone 15 mg/day in a 1:1 allocation ratio in addition to their run-in therapy. General dietary advice was given to all patients. During the treatment phase, biweekly visits were scheduled until Week 24 for clinical assessment. Patients showing increase in HbA1c by >1% or HbA1c >11.5% at Week 12 or those with FBG >14.44 mmol/L in two subsequent visits were withdrawn from the study.

Subject selection criteria

Patients of either sex aged between 18 and 65 years, body weight ≥60 kg, BMI between 20 and 40 kg/m^2, diagnosed with T2DM as defined by ADA criteria and uncontrolled on a combination of metformin and glimepiride or gliclazide were included. Patients were required to have HbA1c between ≥7.5% and ≤13.0%, fasting blood glucose (FBG) >7.22 mmol/L (measured after at least 8 hours of fasting), post-prandial blood glucose (PPG) >10 mmol/L (measured at 2 hours post-lunch or first meal of the day) at screening visit for inclusion in pre-run-in or run-in period. For randomization into the study, patients were required to have HbA1c between ≥7.5% and ≤11.5%, FBG >7.22 mmol/L, and PPG >10 mmol/L post completion of 3 months' run-in period.

Patients with a history of any retinopathy including diabetic retinopathy requiring laser therapy, 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, myalgia, psoriasis, porphyria, rash, scaling, scaling eczema, or G6PD deficiency were excluded.

Patients receiving insulin therapy, or receiving >10 mg of atorvastatin or >20 mg of simvastatin or >10 mg of rosuvastatin or >20 mg of lovastatin or >40 mg of pravastatin, immunosuppressive drugs or any other drug increasing the risk of myopathy were excluded. Patients with recent cardiovascular events, active gastrointestinal or hematological disorders, diabetic ketoacidosis, hypoglycemia unawareness, abnormal renal or liver function or any other significant illness were not included in the study. Patients receiving any concomitant medication that may interact with the action of the study drug or evaluation parameters and pregnant or lactating women or women of child bearing potential not practicing contraception were also excluded.

Randomization and blinding

Randomization codes were generated using a computer generated randomization technique by the sponsor with a block size of 6 or 10. Post-randomization, to maintain the blinding for study treatments, patient specific drug boxes as per randomization codes were provided by the sponsor. Investigators, participants, outcome assessors, and statisticians were blinded to the treatment assignment.

Outcome

The primary outcome measure was glycemic control measured by mean fall in HbA1c and blood glucose from baseline to Week 12 and Week 24. Secondary outcomes included percentage of patients reaching treatment targets (HbA1c <7.5% and/or reduction in HbA1c by ≥0.5% and/or 1%, FBG <7.22 mmol/L, and PPG <10 mmol/L) and changes in lipid profile and body weight from baseline to Week 12 and Week 24.

Safety assessment was based on adverse events (AEs) and changes in laboratory parameters. An AE was defined as any untoward medical occurrence including an abnormal laboratory finding occurring in a trial subject that need not necessarily be related to the study treatment. Patients were encouraged to report AEs spontaneously or in

response to a general non-directed questionnaire. Ophthalmologic examination that included visual acuity test, fundoscopic examination, visual field test, expert slit lamp test and Amsler grid test was performed at screening, baseline, Week 12, and Week 24 by an ophthalmologist at each site. Patients were clinically evaluated for symptoms of bladder cancer at baseline, Week 12 and Week 24.

Statistical methods

A sample size of 105 patients (without drop out) per treatment group was estimated based on the 0.35% between-group difference in change in HbA1c from baseline to Week 24 with 80% power and type I error rate of 0.05.

Statistical analysis was performed on the modified intention to treat (mITT) population which included all patients who completed the study up to at least Week 12 without any protocol violation. The primary efficacy measures were mean change in HbA1c, FBG and PPG from baseline to Week 12 and Week 24 and the difference between groups in these parameters was assessed by using ANCOVA with treatment group as an effect and baseline value as the covariate. Within the framework of the ANCOVA model, point estimates and 95% confidence intervals were calculated for least square mean (LSM) changes within each treatment group. The secondary efficacy parameters (percentage of patients achieving HbA1c <7.5% and/or fall in HbA1c by ≥0.5% and/or ≥1%, percentage of patients achieving FBG <7.22 mmol/L, and percentage of patients achieving PPG <10 mmol/L) were compared using the chi-square test or Fisher's exact test as appropriate. The difference between the two treatment groups in lipid profile and body weight was assessed by using ANCOVA with treatment group as an effect and baseline value as the covariate. Within the framework of the ANCOVA model, point estimates and 95% confidence intervals were calculated for LSM changes within each treatment group from baseline at Week 12 and Week 24. Level of significance was set at 0.05. Safety end points were evaluated for all patients who gave written informed consent for participation in the study. The chi square test was used to compare the percentage of patients reported adverse events.

The last observation carried forward approach was used to impute missing assessments. Statistical analysis was performed using SAS 9.2.

Results

Trial subjects

Of the 806 patients screened, 493 eligible patients entered the 3 months' run-in period. Post 3 months run-in period, 267 eligible patients were randomized to receive either hydroxychloroquine 400 mg/day ($n = 135$) or pioglitazone 15 mg/day ($n = 132$) in addition to two-drug run-in therapy.

One-hundred and ninety-nine patients (hydroxychloroquine group: 100; pioglitazone group: 99) completed the study. Two-hundred and thirty-two patients, who completed the study up to at least 12 weeks without any protocol violation, were included in the mITT population for the efficacy analysis. The disposition of study participants is given in Figure 1.

Demography was well matched, and baseline glycemic characteristics were similar between treatment groups (Table 1).

Efficacy

Primary efficacy parameter: glycemic control

The mean HbA1c significantly reduced after the completion of the run-in period, and it further showed a significant reduction from baseline at Week 12 and Week 24 with the addition of the third drug ($p < 0.0001$) (Table 2). The reduction in mean HbA1c at Week 12 ($p = 0.394$) and Week 24 ($p = 0.909$) was not significantly different between treatment groups.

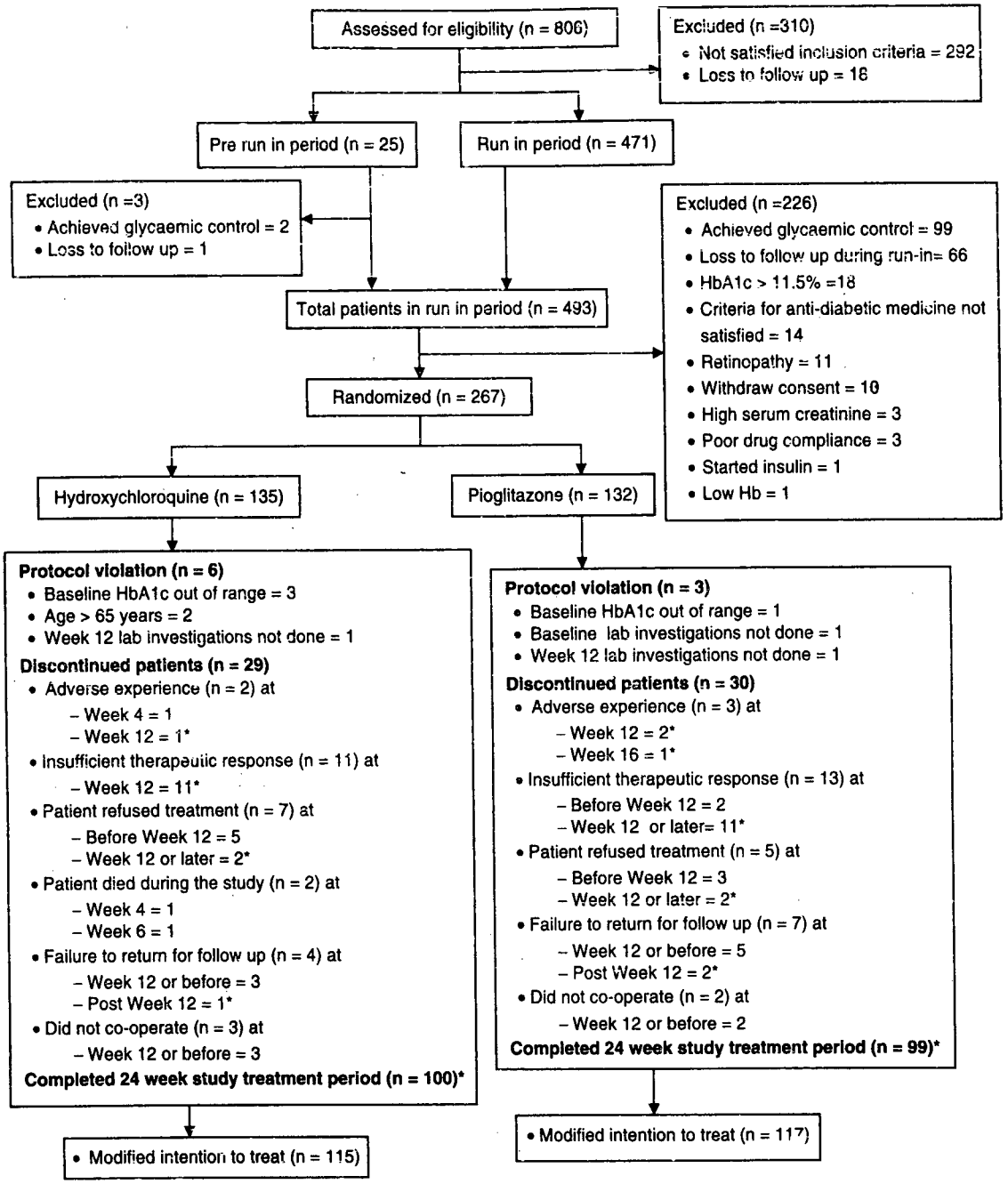
Blood glucose (FBG and PPG) also showed a reduction at baseline from screening and it further reduced at Week 12 and Week 24 with the addition of the third drug. This reduction was significant at Week 12 and Week 24 for both the treatment groups but was not significantly different between treatment groups at Week 12 ($p = 0.878$) and Week 24 ($p = 0.648$).

At Week 12 and Week 24, mean fall in PPG was significant in both the treatment groups. The reduction in PPG was similar between treatment groups at Week 12 ($p = 0.423$) and Week 24 ($p = 0.415$). Table 2 demonstrates the change in glycemic parameters throughout the study.

Secondary efficacy parameters

Lipid profile

TC and LDL levels significantly reduced from baseline in the hydroxychloroquine group at Week 12 (TC: $p = 0.001$; LDL: $p = 0.002$) and Week 24 (TC: $p = 0.004$; LDL: $p = 0.031$) compared to the increase in these parameters in pioglitazone treated patients. The change in TC and LDL at Week 12 and Week 24 was significant in favor of hydroxychloroquine ($p < 0.05$). Triglyceride levels also significantly reduced at Week 12 ($p = 0.006$) and Week 24 ($p = 0.011$) compared to baseline in the hydroxychloroquine group; whereas, in the pioglitazone group, the reduction was significant only at Week 24 ($p = 0.008$). There was no significant change in HDL at Week 12 and Week 24 from baseline in either treatment group. Table 3 shows changes in lipid profile at Week 12 and Week 24.



*-patient included in the modified intention to treat population which comprised of patients who had completed the study till Week 12 without any protocol violation

Figure 1. Disposition of study participants.

Body weight

Though not significant, mean body weight consistently reduced at Week 12 (69.9 kg) and Week 24 (69.3 kg) from baseline (70.4 kg) in the hydroxychloroquine group, whereas pioglitazone group patients showed weight gain at Week 24 (69.8 kg) from baseline (69 kg).

Percentage of patients achieving goal HbA1c and blood glucose levels

At Week 12 and Week 24, the percentage of patients achieving goal HbA1c, i.e. HbA1c <7%, and blood glucose levels (FBG <7.22 mmol/L and PPG <10 mmol/L) and those achieving ≥0.50% or ≥1.0% reductions in

Table 1. Demographic and baseline disease characteristics of enrolled patients.

Parameters	Hydroxychloroquine group ($N = 135$)	Pioglitazone group ($N = 132$)	Total ($N = 267$)	p Value
Sex*				
Male	59 (43.7)	64 (48.5)	123 (46.1)	0.433
Female	76 (56.3)	68 (51.5)	144 (53.9)	
Age (years)†	52.60 (8.55)	52.23 (8.35)	52.42 (8.44)	0.723
Weight (kg)†	69.86 (9.13)	69.30 (8.53)	69.58 (8.83)	0.608
Height (m)†	1.61 (0.05)	1.60 (0.09)	1.60 (0.09)	0.578
Waist circumference (m)†	0.88 (0.20)	0.89 (0.20)	0.88 (0.20)	0.781
Systolic blood pressure (mmHg)†	125.53 (6.89)	125.02 (6.72)	125.28 (6.80)	0.535
Diastolic blood pressure (mmHg)†	80.62 (4.48)	80.48 (5.60)	80.55 (5.05)	0.825
Duration of diabetes (years)†	4.23 (3.80)	4.02 (3.64)	4.13 (3.71)	0.655
HbA1c (%)†	9.2 (1.2)	9.1 (1.1)	9.1 (1.1)	0.739
FBG (mmol/L)†	10.05 (2.85)	9.68 (3.19)	9.87 (3.03)	0.319
PPG (mmol/L)†	14.53 (3.68)	14.44 (3.77)	14.49 (3.72)	0.849
TG (mmol/L)†	1.94 (1.12)	2.00 (1.22)	1.97 (1.17)	0.665
TC (mmol/L)†	4.53 (1.08)	4.70 (1.10)	4.61 (1.09)	0.219
LDL (mmol/L)†	2.57 (0.99)	2.68 (1.01)	2.63 (1.00)	0.379
HDL (mmol/L)†	1.14 (0.27)	1.13 (0.34)	1.13 (0.30)	0.745
Sulfonylurea consumption*				
Glimepiride	111 (82.22)	108 (81.82)	219 (82.02)	0.932
Gliclazide	24 (17.78)	24 (18.18)	48 (17.98)	
Doses of sulfonylurea*				
Glimepiride				
4 mg	83 (61.48)	81 (61.36)	164 (61.42)	0.969
>4 mg	28 (20.74)	27 (20.45)	55 (20.59)	
Gliclazide				
160 mg	14 (10.37)	12 (9.09)	26 (9.75)	0.562
>160 mg	10 (7.40)	12 (9.09)	22 (8.24)	
Doses of Metformin*				
1000 mg	73 (54.07)	71 (53.79)	144 (53.93)	0.963
>1000 mg	62 (45.93)	61 (45.21)	123 (46.07)	

*Values are expressed as n (%); chi square test used for comparison.
†Values are expressed as mean (SD); two sample t test used for comparison.
HbA1c – glycosylated hemoglobin; FBG – fasting blood glucose; PPG – post-prandial glucose, TG – triglycerides, TC – total cholesterol, LDL – low-density lipoprotein, HDL – high-density lipoprotein.
Hydroxychloroquine group: hydroxychloroquine + metformin + glimepiride/gliclazide; pioglitazone group: pioglitazone + metformin + glimepiride/gliclazide.

HbA1c were not significantly different between treatment groups.

Safety

Both the treatments were safe and well tolerated. During the treatment period, 27 patients reported 43 AEs. The detailed list of AEs is given in Table 4. One patient from the hydroxychloroquine group and two patients from the pioglitazone group reported non-proliferative diabetic retinopathy not related to study drugs. None of the patients from the hydroxychloroquine group reported hypoglycemia.

The serious AE of death was reported in two patients from the hydroxychloroquine group: one was due to acute myocardial infarction and the other due to acute pulmonary edema, neither related to study drug in the investigator's opinion and possibly explained by the increased underlying cardiovascular risk in type 2 diabetes patients. Most other AEs were of mild to moderate intensity and were either not related or possibly related to study drugs. Four patients (one from the hydroxychloroquine group and three from the pioglitazone group) reported a rise in serum creatine phosphokinase level but this rise was less than 2.5 times the upper limit of the normal. The causality of these events with respect to the study treatment could not be established by the investigator.

Discussion

Diabetic patients require multiple drugs to control blood sugar levels and to minimize long-term complications associated with diabetes. Concerns have been raised regarding safety issues of recently added anti-diabetic drugs. 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

Table 2. Change in glycemic parameters from baseline at Week 12 and Week 24.

Outcome	Hydroxychloroquine group ($N=115$)	Pioglitazone group ($N=117$)	p Value
Glycemic Parameters			
HbA1c, %			
Screening*	9.70 (1.55)	9.91 (1.4)	0.289
Baseline*	9.03 (0.99)	9.10 (1.08)	0.605
Week 12*	8.48 (1.48)	8.38 (1.76)	0.064
Change from baseline at Week 12†	−0.56 (−0.82 to −0.30)	−0.72 (−0.97 to −0.46)	0.394
p Value‡	<0.0001	<0.0001	
Week 24*	8.18 (1.76)	8.19 (1.97)	0.946
Change from baseline at Week 24†	−0.67 (−1.19 to −0.54)	−0.90 (−1.22 to −0.57)	0.909
p Value‡	<0.0001	<0.0001	
FBG (mmol/L)			
Screening*	10.50 (2.97)	10.60 (3.00)	0.788
Baseline*	9.89 (2.56)	9.63 (3.15)	0.498
Week 12*	8.79 (2.81)	8.68 (2.86)	0.759
Change from baseline at Week 12†	−0.99 (−1.50 to −0.49)	−1.05 (−1.55 to −0.55)	0.878
p Value‡	<0.0001	0.005	
Week 24*	9.01 (3.41)	8.70 (4.43)	0.549
Change from baseline at Week 24†	−0.79 (−1.50 to −0.08)	−1.02 (−1.73 to −0.32)	0.648
p Value‡	0.008	0.046	
PPG (mmol/L)			
Screening*	15.08 (4.25)	15.23 (3.98)	0.787
Baseline*	14.30 (3.53)	14.23 (3.69)	0.884
Week 12*	12.31 (4.15)	12.73 (3.56)	0.413
Change from baseline at Week 12†	−1.93 (−2.62 to −1.23)	−1.52 (−2.22 to −0.83)	0.423
p Value‡	<0.0001	0.002	
Week 24*	12.46 (4.20)	12.89 (3.79)	0.419
Change from baseline at Week 24†	−1.77 (−2.47 to −1.07)	−1.36 (−2.05 to −0.67)	0.415
p Value‡	<0.0001	0.002	

*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 up to at least Week 12 without any protocol violation.

and trends toward reduced insulin resistance and insulin secretion[16]. A previous epidemiological study[6] 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.

Ours was the first clinical study evaluating the anti-hyperglycemic potential of hydroxychloroquine in comparison with pioglitazone in patients inadequately controlled on a combination of glimepiride or gliclazide with metformin. Pioglitazone 15 mg was selected as a comparator because doses above 15 mg are rarely used in Indian patients, in fact pioglitazone 7.5 mg is also approved in India[17]. The advantage of our study design was the inclusion of a run-in period, wherein patients received a combination of glimepiride or gliclazide and metformin and only patients uncontrolled after completion of 3 months' run-in period were randomized to receive a third drug. During the treatment period, the dosage of glimepiride or gliclazide and metformin was kept constant so as to assess the additional effect of the third drug. The rationale for combination therapy is to use multiple agents at their optimal doses (not always the maximum permitted doses) to enhance the safety profile. Therefore, in our study patients taking at least 1000 mg/day of metformin in combination with at least 4 mg/day glimepiride or at least 160 mg/day gliclazide, satisfying eligibility criteria, were randomized to receive a third drug.

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 <6.5 mg/kg/day. The need of annual screening is now reduced to baseline screening and subsequent screening only after 5 years of hydroxychloroquine use. The largest series of rheumatologic patients showed only one case of clear toxicity among 1207 users[18]. 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.

Both the treatment groups were comparable with respect to demography and baseline disease characteristics, thus allowing fair comparison for various efficacy parameters. Our study included comparatively severe diabetes patients as mean HbA1c at baseline was 9.1% and mean

Table 3. Change from baseline in lipid level at Week 12 and Week 24.

Outcome	Hydroxychloroquine group ($N = 115$)	Pioglitazone group ($N = 117$)	p Value
TC (mmol/L)			
Baseline*	4.51 (1.10)	4.65 (1.05)	0.307
Week 12*	4.19 (1.00)	4.71 (1.01)	<0.0001
Change from baseline at Week 12†	−0.37 (−0.53 to −0.21)	0.10 (−0.06 to 0.26)	<0.0001
p Value‡	0.001	0.529	
Week 24*	4.20 (1.11)	4.64 (0.99)	0.002
Change from baseline at Week 24†	−0.37 (−0.55 to −0.19)	0.03 (−0.15 to 0.20)	0.002
p Value‡	0.004	0.886	
TG (mmol/L)			
Baseline*	1.97 (1.09)	2.00 (1.25)	0.835
Week 12*	1.71 (0.88)	1.88 (1.44)	0.255
Change from baseline at Week 12†	−0.28 (−0.49 to −0.08)	−0.12 (−0.32 to 0.08)	0.257
p Value‡	0.006	0.342	
Week 24*	1.71 (0.96)	1.71 (0.98)	0.997
Change from baseline at Week 24†	−0.28 (−0.44 to −0.12)	−0.29 (−0.45 to −0.13)	0.902
p Value‡	0.011	0.008	
LDL (mmol/L)			
Baseline*	2.55 (1.00)	2.63 (0.95)	0.498
Week 12*	2.29 (0.90)	2.67 (0.90)	0.001
Change from baseline at Week 12†	−0.29 (−0.43 to −0.14)	0.08 (−0.07 to 0.22)	0.001
p Value‡	0.002	0.561	
Week 24*	2.35 (0.91)	2.68 (0.91)	0.005
Change from baseline at Week 24†	−0.23 (−0.38 to −0.08)	0.09 (−0.06 to 0.24)	0.003
p Value‡	0.031	0.470	
HDL (mmol/L)			
Baseline*	1.14 (0.26)	1.13 (0.34)	0.950
Week 12*	1.13 (0.31)	1.16 (0.31)	0.547
Change from baseline at Week 12†	−0.00 (−0.05 to 0.05)	0.03 (−0.03 to 0.08)	0.442
p Value‡	0.911	0.413	
Week 24*	1.13 (0.29)	1.18 (0.33)	0.190
Change from baseline at Week 24†	−0.01 (−0.06 to 0.04)	0.05 (0.00 to 0.10)	0.093
p Value‡	0.748	0.084	

*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.
TC – total cholesterol; TG – triglycerides; LDL – low-density lipoprotein; HDL – high-density lipoprotein.
The above analysis was performed on the modified intention to treat population which comprised patients who had completed the study up to at least Week 12 without any protocol violation.

duration of diabetes was 4.1 years compared to the patients evaluated in sitagliptin studies[19,20,21].

As HbA1c is likely to change within 3 months, patients showing increase in HbA1c by 1% or those with HbA1c >11.5% were withdrawn from the study. During the treatment period, there was an incremental reduction in all three glycemic parameters, thus demonstrating the effect of the third drug.

Post 12 and 24 weeks of therapy, reduction in glycemic parameters was not significantly different between treatment groups, thus demonstrating a comparable anti-hyperglycemic profile for hydroxychloroquine and pioglitazone. The possible explanation for the glucose lowering effect of hydroxychloroquine is that the parent drug chloroquine slows insulin clearance, possibly by stabilizing intracellular lysosomes and slowing the breakdown of internalized insulin-receptor complex. This is supported by the fact that hydroxychloroquine inhibits cystosolic insulin metabolizing enzyme[10]. In a study conducted by Rekedal *et al.*[22] in diabetic patients with RA, there was a reduction of 0.66% in baseline HbA1c post 12 months with hydroxychloroquine use. In another study conducted by Gerstein *et al.*[12] in sulfonylurea refractory T2DM patients, a 1.02% reduction in HbA1c was observed with the use of hydroxychloroquine and glyburide for 6 months.

The impact of oral anti-diabetic agents on atherosclerosis, beyond the expected effects on glycemic control, is an increasingly important consideration[23]. Although both the treatment groups showed a significant fall in TG from baseline, only the hydroxychloroquine group showed a significant fall in TC and LDL-C. This reduction in LDL-C and glycemic parameters along with the reported anti-thrombotic properties of hydroxychloroquine[24] could provide it an added advantage in reducing cardiovascular risk. However, this will require further long-term clinical evaluation.

As reported in the literature, in our study as well, pioglitazone treated patients showed weight gain. However,

Table 4. Adverse events reported during the treatment period.

Adverse event*	Hydroxychloroquine group ($N=135$)	Pioglitazone group ($N=132$)	Total ($N=267$)
Ophthalmology related			
Non-proliferative diabetic retinopathy	1	2	3
Other			
Dizziness	1	3	4
Diarrhea	3	1	4
Edema	0	4	4
Dyspepsia	1	2	3
Headache	1	1	2
Hypoglycemia	0	2	2
Localized infection	0	1	1
Nasopharyngitis	1	1	2
Weight increased	0	1	1
Abdominal pain upper	1	0	1
Rise in CPK level	1	3	4
Abnormal feces	0	1	1
Chest pain†	1	0	1
Acute pulmonary edema†	1	0	1
Cough	1	0	1
Rash	0	1	1
Dysfunctional uterine bleeding	1	0	1
Dyslipidemia	1	0	1
Nausea	1	0	1
Pain in extremity	0	1	1
High TG	0	1	1
Paresthesia	0	1	1
Urinary tract infection	1	0	1
Total	17	26	43
Number of patients‡	11 (8.15)	16 (12.12)	27 (10.11)

*Adverse event represented by preferred term. One patient may have reported more than one adverse event.
†Serious adverse event which resulted in patient's death.
‡Value expressed as n (%); p value = 0.284 using chi square test.

hydroxychloroquine treated patients showed weight reduction at Week 24.

Both the treatments were well tolerated without incidence of any drug-related ophthalmology events or development of bladder cancer.

Considering the multifaceted effects of hydroxychloroquine, it could slow down the progression from the pre-diabetes 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.*[9], 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.

Conclusion

Hydroxychloroquine showed comparable hypoglycemic effects to those of pioglitazone as a third-line treatment in T2DM patients inadequately controlled on a combination of glimepiride or gliclazide and metformin. Hydroxychloroquine also showed favorable effects on lipid profile (fall in TC and LDL-C) when compared to pioglitazone and was safe and well tolerated. Based on the multi-faceted effects of hydroxychloroquine on blood glucose, lipid profile, and body weight, hydroxychloroquine may emerge as a well tolerated therapeutic option for T2DM patients uncontrolled on conventional therapy.

Transparency

Declaration of funding

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Declaration of financial/other relationships

A.P. and N.B.C. have disclosed that they are employees of Ipca Laboratories Limited. N.T., V V., A.D., O.P.G., A.S., A.K., S.B., N.K.T., B.S., S.D., N.B.V., S.S., N.A., M.M., and K.K. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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