

Efficacy of Hydroxychloroquine as an Add on Drug with Basal Insulin, Gliclazide and Metformin in Subjects with Uncontrolled Type 2 Diabetes Mellitus

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To cite this article:

Abhishek Kumar Chandra, Sajjad Ahsan, Prakash Ranjan, Ajeet Kumar Sinha, Rajeev Ranjan Kumar. Efficacy of Hydroxychloroquine as an Add on Drug with Basal Insulin, Gliclazide and Metformin in Subjects with Uncontrolled Type 2 Diabetes Mellitus. *International Journal of Diabetes and Endocrinology*. Vol. 3, No. 4, 2018, pp. 58-62. doi: 10.11648/j.ijde.20180304.11

Received: November 25, 2018; **Accepted:** December 11, 2018; **Published:** January 7, 2019

Abstract: The aim of the study was to evaluate the clinical safety and efficacy of hydroxychloroquine in subjects with were poorly controlled type 2 diabetes mellitus (T2DM), despite treatment with insulin glargine and a combination of gliclazide and metformin. 105 patients with type 2 DM, mean age 56.84 years and mean body mass index (BMI) 26.30 kg/m², were enrolled in this multicentre open label trial. They were given hydroxychloroquine 400 mg/day in addition to previous treatment with insulin glargine (≥ 30 units a day), gliclazide (80 mg a day) and metformin (1000 mg a day) for a period of six months. Hydroxychloroquine 400 mg/day, when added to insulin glargine and the combination of gliclazide and metformin, significantly decreased hemoglobin A1c (HbA1c) at six months from a mean of 8.15 ± 0.24 to a mean of 6.69 ± 0.42 ($p < 0.0001$) and fasting plasma glucose (FPG) at six months from a mean of 209.5 ± 31.23 mg/dl to 115.14 ± 36.94 mg/dl and post prandial plasma glucose (PPG) from a mean of 338.22 ± 31.76 mg/dl to 147.71 ± 22.47 mg/dl ($p < 0.0001$). Hydroxychloroquine was well tolerated throughout the study period. The mean dose of insulin glargine decreased during the study from 35.51 ± 9.93 units per day to 20.00 ± 9.6 units/day at six months ($p < 0.0001$). The frequency of insulin glargine injections decreased from a mean of 2.15 ± 0.22 /day to 1.18 ± 0.85 /day ($p < 0.0001$). In 43 (41%) patients insulin glargine had to be totally stopped. In 13 (12%) patients the dose of gliclazide decreased to 40 mg. Hydroxychloroquine was found to improve glycemic control, when given as a fourth drug (quadruple drug therapy) in addition to insulin and the combination of gliclazide and metformin in patients with type 2 DM. In a significant number of patients, insulin therapy could be stopped, and in the rest the dose of insulin and gliclazide could be reduced.

Keywords: Hydroxychloroquine, Insulin, Metformin, Gliclazide, HbA1c, PPG, FPG

1. Introduction

Diabetes mellitus is one of the leading causes of death and disability worldwide [1]. India, the second most populous country of the world, has been severely affected by the global diabetes epidemic [2]. The first nationwide study on the

prevalence of Type-II diabetes mellitus (T2DM) reported 2.1% and 1.5% prevalence in the urban and rural populations of India, respectively [3].

Chronic hyperglycemia in patients with type 2 diabetes

mellitus (DM) occurs because of resistance to the action of insulin and decreasing insulin secretion. Patients with type 2 diabetes are often treated according to a stepped progression, starting with a regimen of nutrition and exercise, and progressing to sulphonylurea, metformin and gliptins alone or in combination. These therapies are often ineffective. The longer the diabetes has been present, the more likely the patients are to require insulin to control their hyperglycemia [4, 5]. Despite insulin treatment, often in high doses, hyperglycemia in these patients is not well controlled [4]. In UKPDS [5], glycemic control deteriorated continuously, even in intensively treated patients with type 2 diabetes.

In order to reduce insulin dose in type 2 diabetes, various studies have been carried out using combination therapies with insulin and sulphonylureas [6, 7], insulin and metformin [8, 9] and insulin in combination with sulphonylureas and metformin [10-12]. The insulin sparing effect of the two drugs, sulphonylurea and metformin, in addition to insulin was 62%, i.e., 1.5- to 2.0-fold effect achieved by the regimens combining either metformin alone or sulphonylureas alone with insulin [10-14].

Hydroxychloroquine has recently approved by DCGI (Drug Controller General of India) to treat type 2 diabetes as add on treatment after metformin and sulphonylurea. Hydroxychloroquine increases insulin availability by partial deactivation of insulin degrading enzyme. Being an acidotropic drug, hydroxychloroquine inhibits insulin degrading enzyme by changing pH of cellular media and therefore may partially increase intercellular insulin availability. Separation of insulin from its receptor is a rate-limiting step. However, HCQ prolongs this dissociation and increases the half-life of insulin [15, 16]. 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 favourable actions on blood glucose, lipid profile and antithrombotic properties, making it an attractive add on therapeutic choice for the treatment of T2DM patients. Even addition of hydroxychloroquine 400mg can reduce the daily insulin dosage almost by 28%, which has demonstrated in recent clinical trial conducted in India by Baidya A et al [17]. It had also being observed in a real word trial, that hydroxychloroquine decreases HbA1c in patients whose type 2 diabetes is poorly controlled with stable-dose insulin therapy with metformin and glimepiride [18]. Ranjan P et. al [19], also confirm that, hydroxychloroquine decreases HbA1c in patients whose type 2 diabetes is poorly controlled with high doses of insulin as compare to Tenueligliptin. Addition of hydroxychloroquine to insulin therapy is also associated with reduced incidence of confirmed and severe hypoglycaemia.

The current trial was conducted to determine whether the addition of hydroxychloroquine 400 mg, could improve the glycemic control in patients with uncontrolled type 2 DM despite therapy with insulin combined with gliclazide and metformin.

2. Subjects and Method

The efficacy of hydroxychloroquine was assessed in a multicentre, open label, prospective and observational trial. Indian men and women aged 40-70 years, body mass index (BMI) 22-35 kg/m², with stable body weight and type 2 DM for at least over one year, high hemoglobin A1c (HbA1c) levels of $\geq 8\%$ and fasting plasma glucose of ≥ 180 mg/dl were included. Patients who were poorly controlled despite combination treatment with gliclazide (80 mg a day) and metformin (1000 mg a day) along with twice a day basal insulin glargine therapy (≥ 30 units a day) for over three months were eligible for recruitment. Patients with clinically significant renal disease, New York Heart Association (NYHA) class III/IV coronary insufficiency or congestive heart failure, symptomatic diabetic neuropathy, diabetic retinopathy/maculopathy, past or present hepatic disease, ketonuria, active infections, and women of child bearing potential were excluded. All subjects signed an informed consent before participation in the study. The protocol was approved by the institution ethics committee of individual centres. The study was conducted in accordance with the Declaration of Helsinki. Patients who met the inclusion criteria were invited to participate in the study. In the beginning, a complete history and physical examination were carried out. A twelve lead electrocardiogram (ECG) was recorded at baseline and after six months. Clinical chemistry was performed on samples with strict quality control. Fasting plasma glucose and post prandial plasma glucose was estimated at baseline and each monthly visit, and HbA1c was estimated at baseline and three and six months. Self-monitoring of blood glucose levels was encouraged.

Patients were given a fixed dose of hydroxychloroquine 400 mg once a day for six months, in addition to insulin glargine, gliclazide and metformin. During the study period, no increase in the dosage of insulin glargine, gliclazide and metformin were allowed. However, a decrease in the dose of insulin glargine and gliclazide, if required, were made when patients had fasting plasma glucose concentration below 90 mg/dl at one office visit, a concentration of 90 to 110 mg/dl on two consecutive office visits, or a concentration of ≥ 100 mg/dl on two consecutive days during self-monitoring at home. Investigations like lipid parameters and C-peptide were not performed due to financial constraints. There was no control group with placebo therapy as the ethics committee did not feel it rational to expose the control group to hyperglycemia for six months. At the end of the study, patients were classified as responders if fasting plasma glucose was ≤ 110 mg/dl and HbA1c $\leq 7.0\%$, and the rest were non-responders.

Statistical Analysis: Statistical analysis was performed using Graph Pad Prism5 version 5.01 statistical software. Student's t-test was used to compare continuous variables (paired t-test for paired data and two-sample t-test for unpaired data). The χ^2 -test was used to compare categorical variables. Multiple logistic regression analysis was performed to determine the variables significantly associated

with responders. The 95% confidence interval (CI) and odds ratio were computed whenever applicable. The analysis of efficacy was performed according to the intention-to-treat method and included all patients who received at least one dose of hydroxychloroquine and had at least one follow up visit. The last observation for patients was carried forward to impute missing values. The safety analysis also included all patients. Data are presented as mean \pm SD. A p value <0.05 was considered statistically significant.

3. Results

Of the 105 subjects recruited, 100 subjects completed the study. Among the patients excluded, three were lost to follow up, one withdrew because of severe gastritis, and in one patient hydroxychloroquine was withdrawn as he developed pigmentation. Clinical characteristics of the 105 subjects at recruitment are summarized in Table 1.

Table 1. Baseline characteristics (intention-to-treat population).

Variables	N= 105
Age (yrs)	56.84 \pm 7.81
Male	49 (47%)
Female	56 (53%)
Diabetes duration (yrs)	9.71 \pm 5.32
BMI (kg/m ²)	26.30 \pm 4.15
Waist-to-Hip Ratio	0.92 \pm 0.08
Body weight (kg)	67.11 \pm 3.79
Fasting plasma glucose (mg/dl)	209.5 \pm 31.23
Post Prandial glucose (mg/dl)	328.3 \pm 31.76
HbA1c (%)	8.15 \pm 0.24

There was a significant decrease in HbA1c (%) at six months from a mean of 8.15 \pm 0.24 to 6.69 \pm 0.42 (p<0.0001) (Table 2); 69 (66%) patients achieved HbA1c \leq 7%. There was a significant decrease in fasting plasma glucose at six months from a mean of 209.5 \pm 31.23 mg/dl to 115.14 \pm 26.11 mg/dl (p<0.0001) and post prandial from mean of 338.22 \pm 31.76 mg/dl to 147.71 \pm 22.47 mg/dl, beginning at one month and reaching maximal effects at six months (Figure 1); 71 (68%) patients achieved fasting plasma glucose of \leq 110 mg/dl.

Table 2. Change from baseline to 24 week study end point.

Variables	N= 100			
	Baseline	After 24 week	Δ Change	p Value
BMI (kg/m ²)	26.30 \pm 4.15	25.46 \pm 3.05	-0.84 \pm 2.19	<0.0005
Body weight (kg)	67.11 \pm 3.79	62.66 \pm 2.87	-4.45 \pm 2.18	<0.0001
Fasting plasma glucose (mg/dl)	209.5 \pm 31.23	115.14 \pm 26.11	-94.36 \pm 21.83	<0.0001
Post Prandial glucose (mg/dl)	338.22 \pm 31.76	147.71 \pm 22.47	-190.51 \pm 19.89	<0.0001
HbA1c (%)	8.15 \pm 0.24	6.69 \pm 0.42	-1.46 \pm 0.38	<0.0001
Mean dose of daily basal Insulin glargine	35.51 \pm 9.93	20.00 \pm 9.6	-15.51 \pm 9.1	<0.0001
The frequency of insulin glargine injections (per day)	2.15 \pm 0.22	1.18 \pm 0.85	-0.87 \pm 0.67	<0.0001

4. Discussion

In the present study, the study sample was significantly

There were 31 (29%) patients who could be classified as responders, who achieved both fasting plasma glucose \leq 110 mg/dl and HbA1c \leq 7%. There was a significant decrease in the mean body weight by 4.45 \pm 2.18 kg (p<0.0001) and BMI by 0.84 \pm 2.19 kg/m² (p<0.0005). There was no statistically significant change in WHR. Hydroxychloroquine was well tolerated throughout the study. There were no clinically significant changes in ECG recordings. Transient elevations greater than 1.5 times the upper limit of normal AST and ALT levels were not observed in any but one study patient. 14 (13%) patients experienced gastritis. No adverse changes in renal function were evident during the study. Symptoms associated with hypoglycemia were reported by 26 (24.7%) patients. Most patients who reported hypoglycemia experienced one episode. No cases hypoglycemia was severe enough to require hospitalization. The mean dose of insulin glargine decreased during the study from 35.51 \pm 9.93 units per day to 20.00 \pm 9.6 units/day at six months (p<0.0001). The frequency of insulin glargine injections decreased from a mean of 2.15 \pm 0.22/day to 1.18 \pm 0.85/day (p<0.0001). In 43 (41%) patients insulin glargine had to be totally stopped. In 13 (12%) patients the dose of gliclazide decreased to 40 mg. There was no change in the dose of metformin during the study.

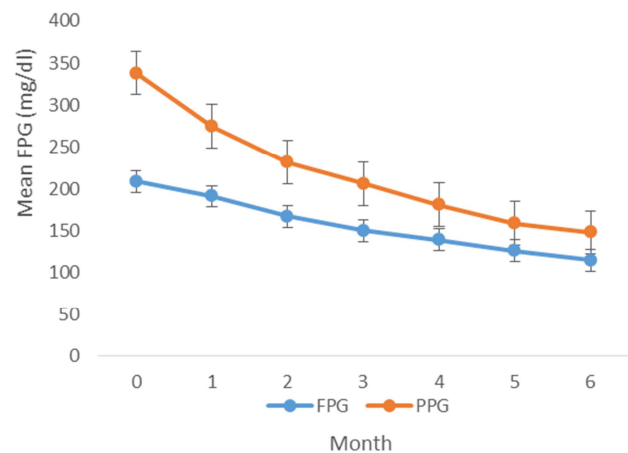


Figure 1. Decrease in mean FPG and PPG (Mean \pm SEM).

hyperglycemic, as evident by the mean baseline HbA1c level of 8.15% and fasting and post prandial plasma glucose level of 209.3 and 338.22 mg/dl respectively. A significant number of patients (n=69; 66%) achieved HbA1c level of \leq 7%.

Similarly, 71 (68%) patients achieved a fasting plasma glucose of ≤ 110 mg/dl. The 6-month duration of the study was intended to provide a sufficient exposure to demonstrate the maximal therapeutic effect, as assessed by reduction in the HbA1c, fasting and post prandial plasma glucose levels. Our study has provided evidence supporting the use of hydroxychloroquine as an add on drug in type 2 diabetes patients with inadequate glycemic control despite the treatment with insulin and combination doses of gliclazide and metformin. The quadruple drug therapy used in the study demonstrated early and sustained reductions in fasting and post prandial glucose levels, followed by reductions in HbA1c levels. A previous study using hydroxychloroquine as a third drug after sulphonylurea and metformin showed similar glycemic efficacy [19].

In this study, ten (22.8%) patients treated with hydroxychloroquine reported symptomatic hypoglycemia. The incidence of reported hypoglycemia was evenly distributed over the entire 6-month study period, suggesting that hypoglycemic symptoms are not directly associated with the initiation of hydroxychloroquine therapy. Hydroxychloroquine therapy can lead to hypoglycemic episodes when used in combination with insulin or insulin secretagogue. Concurrent decrease in insulin doses and insulin secretagogue therapy is warranted when patients experience frank hypo-glycemia or sustained reduction in plasma glucose levels. In the present study there was a significant reduction in the insulin requirement as well as in the frequency of insulin injections, and a decrease in the mean dose of gliclazide. A decrease in insulin requirements may be of interest in diminishing insulin degradation partially and its possible consequences. Insulin therapy had to be totally stopped in 43 (41%) patients.

Our study showed that hydroxychloroquine was effective and well tolerated when used as a fourth drug with sulphonylurea (gliclazide), metformin and insulin. The addition of hydroxychloroquine reduced the requirement of insulin and gliclazide. As the result, a proportion of such patients treated with quadruple drug therapy were able to reach target HbA1c $\leq 7.0\%$ and fasting plasma glucose levels ≤ 110 mg/dl.

Although in this short, 6-month trial we found hydroxychloroquine to be a safe drug, its long-term consequences are not known. In contrast, we have decades of experience with the extensive use of sulphonylureas and metformin. It is therefore rational to use hydroxychloroquine either as a third drug for type 2 DM, after sulphonylurea and metformin, or a fourth drug in patients on insulin and combination of sulphonylurea and metformin, rather than making it the first option drug in therapy of type 2 DM.

5. Conclusion

Our study has shown that hydroxychloroquine is effective in improving the glycemic control when added to a combination of insulin, gliclazide and metformin in type 2 DM. In a significant number of patients, insulin therapy could be stopped and in the rest the dosage of insulin and

gliclazide could be reduced. Hydroxychloroquine is a relatively safe drug and is a valuable addition to the currently available oral antidiabetic agents.

References

- [1] Standards of Medical Care in Diabetes—2014. *Diabetes Care* 2014; 37 (Suppl. 1): S14–S80 Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2014; 37 (Suppl. 1): S81–S90 - March 01, 2014.
- [2] Seema A Kaveeshwar, Jon Cornwall. The current state of diabetes mellitus in India, *Australasian Medical Journal*, Vol 7, No. 1, 45–48, 2014.
- [3] P. K. Patnaik, K. K. Jain, P. Chandra, J. Pathak, K. V Raman, and A. Shah, “Diabetes in India: Measuring the dynamics of a public health catastrophe Current Estimates of Prevalence: Do We Know Enough About Diabetes,” pp. 77–84, 2016.
- [4] Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS. Intensive conventional insulin therapy for type 2 diabetes: metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 1993; 16: 21-31.
- [5] U. K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-52.
- [6] Peters AL, Davidson MB. Insulin plus a sulfonylurea agent for treating type 2 diabetes. *Ann Intern Med* 1991; 115: 45-53.
- [7] Pugh JA, Wagner ML, Sawyer J, Ramirez G, Tuley M, Friedberg SJ. Is combination of sulfonylurea and insulin therapy useful in NIDDM patients? *Diabetes Care* 1992; 15: 953-9.
- [8] Relimpio R, Pumar A, Losada F, Mangas MA, Acosta D, Astorga R. Adding metformin versus insulin dose increase in insulin-treated but poorly controlled type 2 diabetes mellitus: an open-label randomized trial. *Diabet Med* 1998; 15: 997-1002.
- [9] Robinson AC, Burke J, Robinson S, Johnston DG, Elkeles RS. The effects of metformin on glycemic control and serum lipids in insulin treated NIDDM patients with suboptimal metabolic control. *Diabetes Care* 1998; 21: 701-5.
- [10] Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1999; 130: 389-96.
- [11] Yki-Jarvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in patients with non-insulin dependent diabetes mellitus. *N Engl J Med* 1992; 327: 1426-33.
- [12] Chow C-C, Tsang LWW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. *Diabetes Care* 1995; 18: 307-14.
- [13] Riddle MC, Schneider J. Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone: Glimepiride Combination Group. *Diabetes Care* 1998; 21: 1052-7.

- [14] Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, Menheere PP, Nieuwenhuijzen KA. Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care* 1996; 19: 1326-32.
- [15] Pareek A., et al. "Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with pioglitazone". *Current Medical Research and Opinion* 30.7 (2014): 1257-1266.
- [16] Jagnani VK, Bhattacharya NR, Satpathy SC, Hasda GC, Chakraborty S. Effect of hydroxychloroquine on type 2 diabetes mellitus unresponsive to more than two oral antidiabetic agents. *J Diabetes Metab.* 2017; 8: 771.
- [17] Baidya A, Chakravarti HN, Saraogi RK, Gupta A, Ahmed R, et al. Efficacy of maximum and optimum doses of hydroxychloroquine added to patients with poorly controlled type 2 diabetes on stable insulin therapy along with glimepiride and metformin: association of high-sensitive c-reactive protein (hs-crp) and glycosylated haemoglobin (hba1c). *Endocrinol Metab Syndr.* 2018; 7: 283-7.
- [18] Kumar V, Singh MP, Singh AP, Pandey MS, Kumar S, Kumar S. Efficacy and safety of Hydroxychloroquine when added to stable insulin therapy in combination with metformin and glimepiride in patients with type 2 diabetes compare to sitagliptin. *Int J Basic Clin Pharmacol* 2018; 7.
- [19] Ranjan P, Ahsan S, Bhushan R, Kumar B, Tushar, et al. Comparison of Efficacy and Safety of Hydroxychloroquine and Teneeligiptin in Type 2 Diabetes Patients who are Inadequately Controlled with Glimepiride, Metformin and Insulin therapy: A Randomized Controlled Trial with Parallel Group Design. *Ann Clin Endocrinol Metabol.* 2018; 2: 030-040. <https://doi.org/10.29328/journal.acem.1001009>