Original Research Article

Effect of early addition of hydroxychloroquine in type 2 diabetic patients inadequately controlled on metformin and sulfonylurea combination therapy

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ABSTRACT

Background: Present study assessed the effect of early addition of hydroxychloroquine to metformin and sulfonylurea in inadequately controlled T2DM patients as compared to up titration of the metformin or sulfonylurea (glimepiride) doses.

Methods: Patients with glycated haemoglobin (HbA1c) between ≥ 7.0 to $\leq 9.0\%$ and on metformin 1000mg/day and glimepiride 2mg/day for at least 12 weeks were analysed for this study. Patients were randomized into three groups, in one group (n=55) metformin dose was up titrated to 2000mg daily and in second group (n=55) hydroxychloroquine (HCQ) 400mg was added along with other and in third group (n=55) glimepiride dose was up titrated to 4mg. Fasting plasma glucose (FPG), post prandial plasma glucose (PPG) and glycated haemoglobin (HbA1c) were measured at baseline and after 12 and 24 weeks. Low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and Triglyceride were measured at baseline and after 6 months. Authors have analysed the data of 150 patients as rest were either lost in follow up or discontinue therapy.

Results: After 24 weeks, the mean HbA1c was 6.5% in hydroxychloroquine group ($p < 0.001$) versus 6.8% in metformin 2000mg group ($p < 0.001$) and 6.7% in glimepiride 4mg group ($p < 0.001$). There was also a modest reduction in lipid parameters ($p < 0.001$) with no change in serum creatinine level and a marginal reduction in body weight in the HCQ group. Incidence of confirmed hypoglycemia was significantly lower in patients of HCQ group compared to glimepiride group in this study.

Conclusions: Hydroxychloroquine as add on to metformin and glimepiride combination during the early course of treatment helps in achieving glycaemic target and can consider as an option rather up titrating the dose of metformin or glimepiride.

Keywords: Fasting plasma glucose, Glimepiride, Hydroxychloroquine, Metformin, Post prandial plasma glucose, T2DM

INTRODUCTION

Type 2 diabetes mellitus is one of the most common metabolic diseases, with its prevalence increasing worldwide. The pathophysiology of this disease is

characterized mainly by defective insulin secretion and increased insulin resistance. The importance of early blood glucose control was shown in the UK Prospective Diabetes Study (UKPDS), showing that early intensive blood glucose control since the time of diagnosis of

diabetes mellitus reduced micro- and macrovascular complications, as well as mortality.^{1,2} Oral hypoglycemic drugs with various mechanisms, such as enhancing the pancreatic function to secrete insulin, reducing insulin resistance of the body tissues or increasing glucagon-like peptide-1, have been developed and are currently in use.

Considering the compliance and cost-effectiveness, the use of a fixed-dose combination pill of sulfonylurea and metformin has recently increased. Metformin is widely used as an oral agent for the treatment of type 2 diabetes mellitus. It is recommended as an initial monotherapy. It helps in weight loss and has a record of efficacy and safety, with a very low risk of hypoglycaemia.³ The UKPDS suggested a beneficial effect of metformin monotherapy, compared with conventional dietary modification therapy, on cardiovascular disease and mortality after about 10 years in overweight patients with type 2 diabetes.¹ When metformin alone is insufficient, the choice of second-line treatment has remained a challenge and despite a plethora of new agents, sulfonylureas like glimepiride is still the most accepted second-line add-on to metformin, especially in Indian clinical settings. Maximum dose of glimepiride may lead to severe hypoglycemia and weight gain.² Combination therapy using sulfonylurea and metformin, which respectively promotes insulin secretion and improves insulin resistance, is an effective and has complementary mechanisms that improves both of the main causes of type 2 diabetes and has been reported by UKPDS and other clinical studies to be more effective than monotherapy of either drugs.^{4,5}

Hydroxychloroquine is approved by DCGI (Drug Controller General of India) in 2014 as a third line add on treatment in T2DM patient uncontrolled on metformin and sulfonylurea. HCQ most likely acts by reducing the lysosomal degradation of internalised insulin-insulin receptor complex.⁶ This is a novel mechanism of action in contrast to insulin secretagogue or insulin sensitizer action of other antidiabetic drugs. In recent clinical study, it has been observed that HCQ has reduced total daily insulin dose by 28% with 1.3% HbA1c reduction from baseline.⁷ In another trial, uncontrolled type 2 diabetes patients (HbA1c: 7.5-11.5%) on a combination of metformin 1000mg/day and glimepiride 4mg/day or gliclazide 160mg/day were randomized to receive either hydroxychloroquine 400mg/day (n=135) or pioglitazone 15mg/day (n=132) for 24 weeks. There was a significant reduction in the mean HbA1c, FBG and PPG from baseline at week 24 in both the groups.⁸ A marginal weight reduction of 1.08 kg was also reported with hydroxychloroquine in that study. All the trials till now conducted with Hydroxychloroquine 400mg has confirmed its superior potency of HbA1c reduction in uncontrolled T2DM patients.

There was no study comparing the use of hydroxychloroquine, sulfonylurea and metformin combination with up titration of metformin or glimepiride

dose at an early stage in Indian type 2 diabetes patients inadequately controlled on moderate dose of metformin and glimepiride combination therapy.

In this study we assessed the effect of early addition of hydroxychloroquine to metformin and glimepiride combination therapy in inadequately controlled T2DM patients as compared to up titration of the dose of metformin or glimepiride in those patients.

METHODS

One hundred fifty T2DM patients with HbA1c between ≥ 7.0 to $\leq 9.0\%$ and on metformin 1000mg/day and glimepiride 2mg/day for at least 12 weeks were recruited for this study. Initially 180 patients were screened but only 165 patients who matched the inclusion criteria were included in this study, but we have analysed the data of 150 patients as rest 15 patients were discontinued. Patients were randomized into three groups, in first group (Group A, n=55) metformin dose was up titrated to 2000mg daily in addition to glimepiride 2mg and in second group (Group B, n=55) HCQ 400mg was added along with metformin 1000 mg and glimepiride 2mg and in third group (Group C, n=55) glimepiride dose was up titrated up to 4mg in addition to metformin 1000mg. FPG, 2 hours PPG and HbA1c were measured at baseline and after 12 and 24 weeks. LDL-C, HDL and Triglyceride were measured at baseline and after 24 weeks. All the patients were counselled about lifestyle modifications at the baseline and during each follow up visits. All patients have received atorvastatin 10mg once daily for their dyslipidemia management.

Figure 1: Disposition of study participants.

At initial stage, during randomization 15 patients was excluded as they fail to fulfil inclusion eligibility criteria. Among the 15 patients that has discontinued after

randomization, 8 patients in total has withdrawn their consent and 7 patient's violets protocol. Individual group details are elaborated in Figure 1.

Primary objective of the study was to determine the effect on reduction of HbA1c, fasting plasma glucose and post prandial plasma glucose. Secondary objective was to observe percentage of patients achieving HbA1c <7%, incidence of hypoglycemia and change in lipid profile parameters.

Inclusion criteria

Both men and women of type 2 DM, age between 20 years to 70 years, on combination therapy of metformin 1000mg/day and glimepiride 2mg/day for at least for last 3 months with HbA1c of ≥ 7.0 to $\leq 9.0\%$ were included in this study.

Exclusion criteria

Patients with type 1 diabetes mellitus, pre-existing renal, hepatic or cardiac disease, patients with a history or presence of any retinopathy of any grade, patients with known history of diabetic ketoacidosis, glucose-6-

phosphate dehydrogenase deficiency, and known allergy to the drug were excluded from this study. Pregnant and breastfeeding women were also excluded from this study.

Statistical analysis

Statistical analysis was done descriptively for the demographic details. Quantitative data of FPG, PPG and HbA1c from baseline to 12 weeks and 24 weeks were analysed by two-tailed paired t-test for data. Statistical software (Graph Pad Prism5; version 5.01) was used for analysis. Statistical tests were considered significant if P-value was <0.05 at confidence interval of 95%. Statistical significance level was set at P less than 0.05. All study participants provided written informed consent. The study was conducted using good clinical practice and in accordance with the declaration of Helsinki.

RESULTS

Demographics characteristics and baseline biochemical parameters of the three groups are shown in Table 1. Mean age of patients and gender distribution were almost similar in all groups. All group subjects had comparable FPG, PPG and HbA1c at the baseline.

Table 1: Demographic characteristic and base line biochemical parameters of the studied populations.

Characteristics	Group A Metformin 2000mg + Glimepiride 2mg (n=50)	Group B Metformin 1000mg + Glimepiride 2mg + HCQ 400mg (n=50)	Group C Metformin 1000mg + Glimepiride 4mg (n=50)	P value
Gender % (Female)	60%	62%	58%	0.07
Age	49.2 $\pm$ 6.3	49.5 $\pm$ 5.6	50.1 $\pm$ 6.2	0.36
BMI (kg/m ²)	27.8 $\pm$ 4.1	27.8 $\pm$ 4.1	28.1 $\pm$ 3.9	0.19
FPG (mg/dl)	149 $\pm$ 20.4	150 $\pm$ 20.2	152.4 $\pm$ 19.8	0.21
PPG (mg/dl)	240.4 $\pm$ 34.4	242.1 $\pm$ 36.4	244.3 $\pm$ 37.5	0.29
HbA1c (%)	7.9 $\pm$ 0.4	8 $\pm$ 0.4	7.9 $\pm$ 0.4	0.39
Creatinine (mg/dl)	0.72 $\pm$ 0.23	0.72 $\pm$ 0.23	0.70 $\pm$ 0.19	0.75
LDL-C (mg/dl)	139 $\pm$ 12.9	141 $\pm$ 15.4	134 $\pm$ 17.8	0.63
HDL (mg/dl)	45.9 $\pm$ 5.2	42.9 $\pm$ 5.2	44.8 $\pm$ 6.5	0.54
Triglyceride (mg/dl)	189.8 $\pm$ 20.9	192.3 $\pm$ 20.9	190.2 $\pm$ 23.9	0.49

Note: Values are presented as mean $\pm$ standard deviation otherwise mentioned

Patients studied in the different groups had a mean age of 49.52 $\pm$ 6.1 years and 60% were female. Mean HbA1c was 7.9 $\pm$ 0.5%, mean body mass index (BMI) was 27.9 $\pm$ 5.9kg/m² and mean duration of diabetes was 6.2 $\pm$ 2.4 years. High BMI is indicating that all patients were overweight and having long duration of diabetes. There were no significant differences in the baseline characteristics of the three groups of patients (P >0.05, Table 1).

Change in glycemic parameters

Authors have observed a significant reduction in FPG, PPG in all the three groups. In group A FPG was reduced from 149 $\pm$ 10.4 to 119 $\pm$ 10.4, whereas PPG was reduced from 240.4 $\pm$ 24.4 to 156.4 $\pm$ 14.1. In group B FPG was reduced from 150 ($\pm$ 10.2) to 109.4 ($\pm$ 10.8), whereas PPG was reduced from 242.1 ($\pm$ 26.4) to 138.4 ($\pm$ 12.5). In group C FPG was reduced from 152.4 $\pm$ 10.8 to 121.4 $\pm$ 9.8, whereas PPG was reduced from 244.3 $\pm$ 21.5 to 152.4 $\pm$ 11.5 (Table 2). Comparison of fasting plasma

glucose post prandial plasma glucose has demonstrated in Figures 2 and 3.

Figure 2: Comparison of fasting plasma glucose from baseline to 24 weeks.

Figure 3: Comparison of post prandial plasma glucose from baseline to 24 weeks.

Authors have also observed a significant reduction in HbA1c. Subjects who received high dose of metformin has recorded 1.1% reduction in HbA1c and the subjects

who received high dose of glimepiride has recorded 1.3% reduction in HbA1c. In HCQ group there was a further HbA1c reduction of 1.5% from baseline (Table 2) (Figure 4).

Figure 4: Comparison of glycated haemoglobin (HbA1c) from baseline to 24 week.

Percentage of patients with HbA1c <7%

Efficacy was further assessed by determining the proportion of subjects who achieved an A1C <7.0% at week 24 of the study. The proportion of subjects was almost similar for both groups 49.4% of glimepiride treated subjects compared with 43.1% of metformin treated subjects (P=0.347). But 61% patients who received HCQ 400 has achieved an A1C <7.0% (Table 3).

Incidence of hypoglycemia

The analysis showed that the risk of confirmed hypoglycemia was significantly lower in patients treated with hydroxychloroquine 400mg and metformin 2000mg group compared with patients group who was on glimepiride 4mg/day for their entire study duration.

Table 2: Changes in the BMI and biochemical parameters of patients between baseline and 24 weeks.

Characteristics	Group A Metformin 2000mg+Glimepiride 2mg (N=50)			Group B Metformin 1000mg+Glimepiride 2mg + HCQ 400mg (N=50)			Group C Metformin 1000mg+Glimepiride 4mg (N=50)		
	Baseline	6 months	P Value	Baseline	6 months	P Value	Baseline	6 months	P Value
BMI (kg/m ²)	27.8±4.1	27.6±3.8	0.0471	27.8±4.1	26.3±2.4	0.0031	28.1 ±3.9	28.9 ±3.8	0.0341
FPG (mg/dl)	149±10.4	119±10.4	<0.001	150±10.2	109.4±10.8	<0.001	152.4±10.8	121.4 ±9.8	<0.001
PPG (mg/dl)	240.4±24.4	156.4±14.1	<0.001	242.1±26.4	138.4±12.5	<0.001	244.3±21.5	152.4±11.5	<0.001
HbA1c %	7.9±0.4	6.8±0.5	<0.001	8.0 ±0.4	6.5±0.5	<0.001	7.9 ±0.4	6.6 ±0.5	<0.001
Creatinine (mg/dl)	0.72±0.16	0.70±0.14	NS	0.72±0.13	0.72±0.13	NS	0.70±0.15	0.78±0.11	NS
LDL-C (mg/dl)	139±12.9	136±13.9	NS	141 ±15.4	126±13.9	<0.001	134 ±17.8	136 ±18.8	NS
HDL (mg/dl)	45.9±5.2	46.6±4.9	NS	42.9±5.2	47.6±4.7	<0.001	42.8±6.5	44.7 ±4.4	NS
Triglyceride (mg/dl)	189.8±20.9	188.8±19.9	NS	192.3±20.9	178.8±19.9	<0.001	190.2±23.9	189.2±23.9	NS

Table 3: Mean reduction in glyceimic parameters compared to baseline after 24 weeks.

Category (n=50)	FPG (mg/dL)	PPG (mg/dL)	HbA1c (%)	% of patients achieved HbA1c <7%
Group A: Metformin 2000mg + Glimepiride 2mg	30.0±10.4	84±14.35	1.1±0.5	43.10%
Group B: Metformin 1000mg + Glimepiride 2mg + HCQ 400mg	40.6±10.3	103.7±13.8	1.5±0.5	61%
Group C: Metformin 1000mg + Glimepiride 4mg	31.0±10.1	91.9±12.7	1.3±0.5	49.40%

The incidence of clinically relevant hypoglycemia was similar for HCQ 400 group and metformin 2000 groups (2% with HCQ vs. 6% with metformin). There were almost 16% patients in glimepiride 4mg group has encountered with clinically relevant hypoglycemia (Table 4). No patients taking any of the combination required medical assistance for symptomatic hypoglycemia. No patients taking any of the combination experienced severe symptomatic hypoglycemia.

Change in lipid profile

There was a significant change in LDL-C, HDL-C and Triglyceride level in HCQ treated group of patients. But in both the metformin 2000mg group and glimepiride 4mg group of patients no significant change was observed in any of the measured lipid parameter values (Table 4).

There was no significant change in body weight or BMI and serum creatinine level in group A. In group B patient's addition of HCQ 400mg has reduced BMI from 27.8±4.1 to 26.3±2.4. There is slightly increase in BMI from 28.1±3.9 to 28.9±3.8 in Group C patients who were treated with high dose of glimepiride (Table 4).

All patients tolerated drugs well without any serious adverse effects. The incidence of gastro-intestinal adverse events was more in high dose metformin group than addition of HCQ group however it was not statistically significant. Ophthalmological examination was conducted after 24 weeks in all the groups and found normal. There was no report of withdrawals or treatment-emergent adverse events related to the study medications, during the treatment phase.

Table 4: Patients having hypoglycemia during study.

Hypoglycemia type	Group A Metformin 2000mg + Glimepiride 2mg (n=50)	Group B Metformin 1000mg + Glimepiride 2mg + HCQ 400mg (n=50)	Group C Metformin 1000mg + Glimepiride 4mg (n=50)
All episode of hypoglycemia	3 (6%)	1(2%)	8 (16%)
Asymptomatic hypoglycemia	1(2%)	0	1(2%)
Symptomatic hypoglycemia	1(2%)	1(2%)	4 (8%)
Nocturnal hypoglycemia	1(2%)	0	3 (6%)
Severe hypoglycemia	0	0	0

DISCUSSION

Type 2 diabetes is a chronic disease that usually requires treatment with multiple anti-hyperglycemic agents during the course of the disease. European Association for the Study of Diabetes and American Diabetes Association guidelines have recommended metformin as a first line drug to be used in type 2 diabetes mellitus patient.

Metformin is a biguanide that suppresses basal hepatic glucose uptake and increases insulin-mediated glucose uptake in peripheral muscle. Because metformin does not stimulate insulin secretion, hypoglycemia is uncommon

with monotherapy, making it an attractive agent for use in T2DM patients.⁹ Among sulfonylureas (SUs) mainly glimepiride is frequently used in treatment in type 2 diabetes patients in India. However, SUs often increases the risks of hypoglycemia and weight gain resulting in deterioration of glyceimic control in the long term.

Hydroxychloroquine is the hydroxyl derivative of chloroquine. It is used, either alone or in combination with other agents, in the management of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other autoimmune diseases.¹⁰ HCQ most likely acts by reducing

the lysosomal degradation of internalised insulin-insulin receptor complex.^{6,10}

In an observational trial there was a further 1.3% reduction in HbA1c as compared to vildagliptin in patients inadequately controlled on metformin and glimepiride.¹¹ In another trial, HCQ 400 was evaluated against teneligliptin in T2DM patients uncontrolled on metformin and glimepiride combination, where the reduction of HbA1c was comparable in both the groups.¹² A double-blinded, randomized study of 267 patients with uncontrolled T2DM was conducted by Pareek et al.⁸ That study conclusively showed that hydroxychloroquine had a similar anti-hyperglycaemic effect as pioglitazone among the patients refractory to metformin and sulfonylurea treatment. Based on this study, hydroxychloroquine 400mg has been officially approved by drug regulatory authority of India to improve glycemic control of T2DM patients on metformin, sulfonylurea combination as an adjunct to diet and exercise therapy. In recent clinical study, it has been shown that HCQ has reduced total daily insulin dose by 28% with 1.3% HbA1c reduction from baseline in patients with poorly controlled type 2 diabetes on stable insulin therapy along with glimepiride and metformin.⁷

In this study we had noticed a significant HbA1c reduction with addition of HCQ 400mg in patients uncontrolled on glimepiride 2mg and metformin 1000mg. This reduction of HbA1c was higher than the up titration of either metformin or glimepiride dose.

Most of the clinical practice guidelines for glycemic control target for type 2 diabetes since the early 2000s have recommend the achievement of near-normoglycemia to prevent diabetes related vascular complications and glycemic goals of HbA1C $\leq 7.0\%$ should be attained in type 2 diabetes mellitus without severe complications or hypoglycemia.^{13,14} However, three recently published large randomised control trials (ACCORD, ADVANCE, VADT) have demonstrated no significant benefits in cardiovascular outcome with intensive glycemic control in type 2 diabetes and participants in the ACCORD and ADVANCE trials and the VADT had type 2 diabetes mellitus for 8.0 to 11.5 years.¹⁵ So, the glycemic target range for patients with type 2 diabetes mellitus should be individualized according to age; stage of disease, both in terms of duration and presence of macro- and microvascular complications; and propensity for hypoglycemia.^{16,17} Participants in this study had type 2 diabetes mellitus for mean 6.2 years and in the practical points, more patients reached an HbA1c level of 7% or less with hydroxychloroquine 400mg plus glimepiride 2mg plus metformin 1000mg than with other two groups where either metformin or glimepiride dose had up titrated.

In contrast to the SUs that stimulate insulin secretion in a glucose-independent manner, increase insulin secretion capacity even at low glucose concentrations,

hydroxychloroquine reduces insulin degradation by altering cellular pH and most likely acts by reducing the lysosomal degradation of internalised insulin-insulin receptor complex. For this unique mechanism of action HCQ deliver fewer hypoglycemic episode as compare to glimepiride.

This study once again confirms that, HCQ 400mg add-on to metformin and glimepiride combination during the early course of treatment would be a multimodal approach in treatment of diabetic patients. Further, it could help in delaying the insulin initiation.

However, all the agents exert unique pleiotropic effects and reduction in glycemic profile, which suggests a theoretical basis for potential benefits through combining therapy. A large-scale clinical trial on reduction in glycemic parameters and cardiovascular events is required to further establish this hypothesis.

CONCLUSION

The addition of hydroxychloroquine to metformin and glimepiride treatment was effective and well tolerated. Hydroxychloroquine add on to metformin and glimepiride combination during the early course of treatment helps in achieving glycaemic target and can consider as an option rather than up titrating the dose of metformin or glimepiride.

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