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Original Research Article

A Hospital-Based Assessment of Efficacy and Safety of Hydroxychloroquine and Teneligliptin in Patients of Type 2 Diabetes Mellitus Refractory to Concomitant Metformin and Glimepiride: A Prospective Comparative Clinical Study

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Abstract

Aim: The aim of the present study was to compare efficacy and safety of Hydroxychloroquine (HCQ) and Teneligliptin in patients of T2DM who are refractory to concomitant Metformin and Glimepiride over a period of 3 months, to evaluates percentage of patients reaching treatment targets i.e., HbA1C <7.5% and/or reduction in HbA1C by 0.5% and/or 1%, FBS - 126mg/dl and PPG- 180mg/dl and changes in BMI and to assess quality of life.

Methods: This was a prospective, randomized, open label study conducted in Department of Pharmacology in collaboration with department of medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India for one year. A total of 100 patients suffering from T2DM visiting the outpatient department of medicine and fulfilling the inclusion criteria were recruited in the study after taking an informed consent.

Results: In this present study we have analyzed a data of 100 patients. 44% were males and 56% were females out of the entire patient population. At the end of 90 days, Group A had shown statistically better ($p<0.005$) effect in improving the BMI as compared to Group B. A highly significant ($p<0.01$) reduction was seen over 90 days in both the groups in Glycaemic parameters i.e., FBS, PPG and HbA1c. Both groups had comparable ($p>0.05$) safety profile with no serious adverse effects and no significant change ($p>0.05$). There was highly significant improvement ($p<0.001$) in VAS scale indicating improvement in quality of life in Group A and B over a period of 90 days.

Conclusion: On the basis of effects of HCQ on the glycaemic parameters and BMI, HCQ may be preferred over Teneligliptin in patients of T2DM who are refractory to concomitant Metformin and Glimepiride**.**

Keywords: Oral hypoglycemic agents, Sulfonylurea, Fasting blood glucose, Visual analogue scale

Introduction

Diabetes mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose, which over time causes both microvascular and macrovascular complications. Diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. [1] The incidence of diabetes has increased by multiple folds over the past 40 years in India. Over this time, rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India. [2] The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. The key management goals of type 2 diabetes mellitus (T2DM) are to achieve target glycemic control (HbA1c ≤ 7%) and prevention of long term complications, whilst avoiding hypoglycaemia. [3] As per American Diabetes Association (ADA) 2016 Guidelines [4], lowering A1c below or around 7.0% has been shown to reduce microvascular and macrovascular complications (if implemented soon after diagnosis). When treatment goals are not achieved with lifestyle modifications and strict dietary regimen, pharmacological treatment is advised. To optimize the management of type 2 DM, several oral antihyperglycemic agents are available. . Lifestyle modifications must be combined with oral hypoglycemic agents (OHA) for optimal glycemic control. American diabetes association suggests that each new class of oral hypoglycemic agents added to initial therapy generally lowers HbA1c, approximately 0.7-1.0%. If the HbA1c target is not achieved after approximately 3 months then start with dual therapy. [4] If HbA1C target is still not achieved after 3 months of dual therapy then proceed to the three drug combination and again, if HbA1c target is not achieved after 3 months of triple therapy, then proceed to combination therapy with insulin. [5]

Metformin and sulfonylureas (SU) are the most commonly used oral antidiabetic agents. However, SU have a greater tendency to cause hypoglycaemia and weight gain and hence, many patients will eventually need to be shifted to another class of oral antidiabetic agents or insulin therapy. [6] Neither sulfonylureas nor metformin are able to preserve ß-cell function, and many patients with type 2 diabetes fail to reach target [glycosylated hemoglobin (HbA1c) <7.0%], despite combined metformin/ sulfonylurea therapy. [7,8] Hence, many patients with type 2 diabetes will eventually require insulin therapy.

Teneligliptin is a recently developed oral dipeptidyl peptidase 4 (DPP-4) inhibitor indicated for the treatment of T2DM in adults along with diet and exercise. [9] It inhibit the enzyme DPP-4 and prolong the action of glucagon-like peptide. This inhibits glucagon release, increases insulin secretion, and decreases gastric emptying thus decreasing blood glucose levels.

Hydroxychloroquine (HCQ), a long-standing safe and inexpensive treatment for autoimmune disorders. HCQ is derived from chloroquine, which has an insulin-sparing effect in T2DM. Hydroxychloroquine has a novel mechanism of action, i.e., post receptor inhibition of insulin degradation for reducing blood glucose levels. Reduction in FBG, PPG and HbA1C (0.87-3.3%) is established in various settings. [10,11] It acts by inhibiting the insulin degrading enzyme and increasing the insulin concentration and decreasing glucose levels. Because of its anti-hyperglycemic potential, anti-inflammatory activity and pleiotropic effects such as lipid lowering action, antiplatelet action, antithrombotic action and nephroprotective action, it may emerge as a cost-effective therapeutic

option for uncontrolled diabetes patients. Hydroxychloroquine 400 mg is approved by DCGI (Drug Controller General of India) and recommended by RSSDI (Research Society for the Study of Diabetes in India) clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in T2DM patients. HCQ was selected for the study because it has a well-established safety profile and have multifaceted effects too such as slow down the progression from the prediabetes stage to diabetes and it can also improve the cardiovascular risk profile in patients of diabetes with its favorable actions on blood glucose, lipid profile, antithrombotic properties and anti-inflammatory properties, making it an attractive therapeutic choice for the treatment of T2DM patients.10 Teneligliptin was selected for the study because it has longer plasma half-life, dual mode of elimination, cost-effective in India when compared to other DPP-4 inhibitors, resulting in better compliance. Teneligliptan and metformin combination results in lowering of glycaemic and lipid profile with reduced side effects of hypoglycaemia and weight gain. Hence, the aim of study was to evaluate the efficacy and safety of two drugs i.e., HCQ and Teneligliptin are compared in combination with Metformin and Glimepiride on glycaemic parameters and their effect on quality of life in patients of T2DM over a period of 3 months, to evaluates percentage of patients reaching treatment targets i.e., HbA1C <7.5% and/or reduction in HbA1C by 0.5% and/or 1%, FBS -126mg/dl and PPG- 180mg/dl and changes in BMI and to assess quality of life.

Material & Methods

This was a prospective, randomized, open label study conducted in Department of Pharmacology in collaboration with department of Medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India for one year. A total of 100 patients suffering from T2DM visiting the outpatient department of medicine and fulfilling the inclusion criteria were recruited in the study after taking an informed consent.

Inclusion Criteria

- Patients diagnosed with T2DM and uncontrolled on a combination of metformin and glimepiride,
- Patients of either sex aged between 18 and 65 years and patients with: HbA1C between 7.5% and 13.0%, fasting blood sugar (FBS) >126 mg/dl (7mmol/l) (measured after at least 8 hours of fasting) and post-prandial blood glucose (PPG) >180mg/dl (10mmol/l) (measured at 2 hours post-lunch or first meal of the day) at screening visit.

Exclusion Criteria

- Patients receiving insulin therapy, or receiving immunosuppressive drugs or any other drug increasing the risk of myopathy.
- Patients with recent cardiovascular events, active gastrointestinal or hematological disorders, diabetic ketoacidosis, hypoglycemia unawareness, abnormal renal or liver function or any other significant illness.
- Patients with a H/O 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.
- H/O myalgia, H/O psoriasis, porphyria, rash, scaling eczema and 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

Patients were randomly divided into 2 groups; A and B consisting of 50 patients each. Randomisation was carried out with the help of random numbers generated by computer software programmer (Random number generator).

Group A received HCQ 400mg OD, Metformin 1 gm BD and Glimepiride 4 mg OD for 90 days. Group B received Teneligliptin 20mg OD, Metformin 1gm BD and Glimepiride 4 mg OD for 90 days.

Follow up was done every 15 days for 90 days for assessment of anthropometric parameters, fasting blood sugar (FBS), Post prandial glucose (PPG), HbA1c, Complete blood count (CBC), Liver function test (LFT), Renal function test (RFT), Adverse drug reactions (ADRs) and Visual analogue scale (VAS).

Statistical Analysis

All the parameters were recorded, tabulated and analysed using 't' test; paired `t`- test for intragroup comparison and unpaired `t` test for intergroup comparison.

Results

Table 1: Demographic details

Gender	N%
Male	44 (44)
Female	56 (56)

In this present study we have analyzed a data of 100 patients. 44% were males and 56% were females out of the entire patient population.

Table 2: Intergroup comparison of various parameters at day '0'

Parameters	Group A (Mean±SD)	Group B (Mean±SD)	P value
Age	54.4±9.1	54.7±10.0	0.940
BMI (kg/m^2)	24.0±2.5	25.05±2.9	0.425
FBS (mg/dl)	190±24.6	188.2±21.0	0.525
PPG (mg/dl)	232.8±14.6	238.2±15.5	0.115
HbA1c (%)	8±0.71	8.2±0.82	0.575
Hb (g/dl)	10.4±1.4	10.8±1.6	0.924
TLC (/cmm)	7082.8±1478.2	7024.6±1415.5	0.845
Monocytes (%)	4.8±2.1	4.4±2.4	0.520
Eosinophils (%)	3.3±1.1	3.2±1.7	0.365
Lymphocytes (%)	28.2±4.6	29.1±5.2	0.425
Platelets count (x10^9/l)	301.9±60.6	284.6±55.5	0.240
S. Bilirubin (mg/dl)	0.32±0.25	0.26±0.24	0.158
SGOT (U/l)	24.0±6.2	22.8±8.2	0.448
SGPT (U/l)	24.6±6.2	24.7±6.3	0.834
S. Albumin (g/dl)	4.0±0.12	4.0±0.18	0.725
Alk_Phosp (IU/l)	197.3±55.0	172.1±72.8	0.135
B.urea (mg/dl)	18.0±2.4	18.0±2.6	1.0
S. Creatinine (mg/dl)	0.86±0.14	0.82± 0.18	0.812
VAS	49.1±6.4	46.4±6.8	0.225

Baseline population and clinical characteristics of the study participants was comparable in both the groups.

Table 3: Intragroup comparison of glycemic parameters in Group 'A' and Group 'B'over '90' days of treatment

Parameters	Baseline	90 days	% Change	P value
FBS (mg/dl)	190±24.6	166.2±25.4	23.8±0.8	<0.001
PPG (mg/dl)	232.8±16.4	194.4±17.3	38.4 ±0.9	<0.001
HbA1c (%)	8±0.71	7.86±0.94	0.14±0.23	<0.001
Parameters	Baseline	90 days	% Change	P value
FBS (mg/dl)	188.2±21.0	168.2±23.7	20.0±2.7	<0.001
PPG (mg/dl)	238.2±15.5	202.8±20.5	35.4±5.0	<0.001
HbA1c (%)	8.2±0.72	8.0±0.88	0.20±0.16	<0.001

At the end of 90 days, Group A had shown statistically better ($p<0.005$) effect in improving the BMI as compared to Group B. A highly significant ($p<0.01$) reduction was seen over 90 days in both the groups in Glycaemic parameters i.e., FBS, PPG and HbA1c.

Table 4: Comparison of adverse effect profile of patients in group 'A' and 'B' over '90' days of treatment

Adverse effect	Group A		Group B	
	N	%	N	%
Tiredness	15	30	-	-
Dizziness	-	-	6	12
Headache	12	24	10	26
Bloating	-	-	12	24
Abdominal pain	7	14	-	-
Constipation	-	-	6	12
Total number	34	-	34	-

Both groups had comparable ($p>0.05$) safety profile with no serious adverse effects and no significant change ($p>0.05$).

Table 5: Intragroup comparison of VAS of patients in group 'A' & 'B' over '90' days of treatment

Time		Group A			Group B		P value
	Mean±SD	Mean change from Day '0'	P value	Mean±SD	Mean change from Day '0'	P value	
At 0 day	44.46±6.55	-	-	44.46±6.55	-	-	
At 90 day	79.41±12.18	32.0±10.40	<0.001**	76.44±10.45	30.0±10.46	<0.001**	>0.05

There was highly significant improvement ($p<0.001$) in VAS scale indicating improvement in quality of life in Group A and B over a period of 90 days.

Discussion

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and second common indication of liver transplantation. It is characterised by excessive hepatic fat accumulation, associated with insulin resistance. If left untreated it can progress to end stage liver disease and hepatocellular carcinoma. [12] The increasing global prevalence of NAFLD, amounting to 55.5% in T2DM, is placing a greater burden on healthcare resources. [13] India showed the prevalence of NAFLD of about 72.4% in northern states of India, with about 48% in Amritsar, district of Punjab, India. [14] The coexistence of NAFLD and T2DM could be

explained by its bidirectional relationship and the sharing of the risk factors such as obesity, insulin resistance and dyslipidaemia. The insulin resistance plays a pivotal role in pathogenesis of NAFLD and T2DM. The exacerbation of hepatic and peripheral insulin resistance in NAFLD and the release of pro-inflammatory cytokines and hepatokines promotes the development of T2DM. Likewise the coexistence of T2DM with NAFLD increases the likelihood of progression of NAFLD to NASH . [15]

In this present study we have analyzed a data of 100 patients. 44% were males and 56% were females out of the entire patient population. At the end of 90 days, Group A had shown statistically better ($p<0.005$) effect in improving the BMI as compared to Group B. The results are similar to a multicentric study of 12 weeks conducted by Pareek et al which showed significant reduction ($p<0.05$) in weight after addition of HCQ (400 mg) with Metformin (1000mg) and Glimepiride (4 mg). [10] A highly significant ($p<0.01$) reduction was seen over 90 days in both the groups in Glycaemic parameters i.e., FBS, PPG and HbA1c. Both groups had comparable ($p>0.05$) safety profile with no serious adverse effects and no significant change ($p>0.05$). These findings are in concordance with a multicentric study of 24 weeks (n=200) conducted by Jagnani et al at tertiary care clinics of Ranchi, Jharkhand and Kolkata, West Bengal, India. This study observed significant mean reduction in FBS (46±25 mg/dl), PPG (78±37 mg/dl) and HbA1c (1.8±1.1) in HCQ (400 mg/day) group ($p<0.001$). Similarly mean reduction in FBS (40±31 mg/dl), PPG (72±32 mg/dl) and HbA1c (1.6±1.1) ($p<0.001$) was observed in Teneligliptin (20 mg/day) group. [16] But in contrast to present study the intergroup difference for the mean change in FBS, PPG and HbA1c from baseline to 24 weeks between HCQ and Teneligliptin groups was also statistically significant ($p\leq0.001$), which indicated the superiority of HCQ in reducing glycaemic parameters. [17]

Both groups had comparable ($p>0.05$) safety profile with no serious adverse effects and no significant change ($p>0.05$). A multicentric study of 12 weeks conducted by Pareek et al (n=267) across India between December 2009 and July 2013 have mentioned about the adverse effects of HCQ. [10] There was highly significant improvement ($p<0.001$) in VAS scale indicating improvement in quality of life in Group A and B over a period of 90 days. We could not find a similar study comparing the effects of concomitant therapies on quality of life as assessed in the present study. Hence, both Group A and B showed improvement in the Glycaemic parameter, BMI and VAS (quality of life) over a period of 90 days. Group A has better effect on BMI. While both groups showed equivalent and beneficial effect on diabetic parameters and VAS. Overall assessment of safety demonstrated that both HCQ and Teneligliptin were well tolerated in this study.

Conclusion

From these observations it can be concluded that Group A was statistically better than group B in reducing BMI. Both the groups showed comparable improvement in FBS, PPG, HbA1c, safety and VAS score. It has been noted that in group A there was a significant number ($p<0.05$) of patients who achieved target glycaemic control (HbA1c $\leq$7.5%). Hence, on the basis of effects of HCQ on the glycaemic parameters and BMI, HCQ may be preferred over Teneligliptin in patients of T2DM who are refractory to concomitant Metformin and Glimepiride.

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