Research Article

Efficacy of bromocriptine mesylate as add-on oral antidiabetic agent in type 2 diabetes mellitus

Kapil Kumar Garg, SN Chugh

Department of Internal Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

Correspondence to: Kapil Kumar Garg, E-mail: kapilgarg81@gmail.com

Received: December 16, 2016; **Accepted:** January 27, 2017

ABSTRACT

Background: There is a need for new oral antidiabetic agents with different modes of action. Moving away from conventional "Triumvirate," most important player implicated in the pathogenesis of type 2 diabetes is the brain, which along with seven other companions form the "ominous octet." Bromocriptine mesylate is one such drug which acts on brain, upregulating dopaminergic tone thereby reducing insulin resistance and improving glucose tolerance. **Objectives:** To study the efficacy of bromocriptine mesylate as an add-on therapy in patients with T2DM inadequately controlled on two oral antidiabetic drugs**. Materials and Methods:** A total of 50 patients according to inclusion and exclusion criteria formed the subject matter of this prospective, non-randomized study. Bromocriptine mesylate was added in weekly 0.8 mg increments to achieve a target dose between 1.6 and 4.8 mg depending on the patient tolerance. Baseline measurements of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycosylated hemoglobin (HbA1c) were followed up at 6 and 12 weeks. Appropriate history, examination and laboratory tests were done at each visit to identify any adverse effects. Paired Student's *t*-test was used for analysis using SPSS 17 statistical software. **Results:** Baseline mean FBS, PPBS, and HbA1c values were 146.86 mg/dL, 227.92 mg/dL, and 8.66%, respectively. After 6 weeks of bromocriptine mesylate add-on therapy, FBS, PPBS and HbA1c showed a mean fall of 19.96 mg/dL, 45.90 mg/dL, and 0.85%, respectively, which was found to be statistically significant ($P < 0.05$). After 12 weeks of therapy, FBS, PPBS, and HbA1c showed a mean fall of 34.24 mg/dL, 60.36 mg/dL, and 1.56%, respectively, when compared with baseline values, was found to be statistically significant ($P < 0.05$). **Conclusion:** Patients showed a significant reduction in fasting, PPBS and HbA1c levels both at 6 and 12 weeks without any significant adverse effects. Reduction in HbA1c was more in diabetics with poor baseline glycemic control compared to those having fair and good control. Bromocriptine mesylate is an effective antidiabetic drug which when added on to existing oral antidiabetic therapy in uncontrolled diabetes helps achieve optimal glycemic control.

KEY WORDS: Diabetes Mellitus; Glycosylated Hemoglobin A; Insulin Resistance; Dopamine Agonists; Bromocriptine

Access this article online	
Website: http://www.ijmsph.com	**Quick** Response code
DOI: 10.5455/ijmsph. 2017.1268827012017	

INTRODUCTION

The World Health Organization defines diabetes mellitus as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, and insulin action or both.[1] The chronic

hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[2]

Type 2 diabetes mellitus (T2DM) constitutes 90% of diabetes cases and its prevalence is increasing at alarming rate worldwide. Management of T2DM is a challenge due to its progressive nature. Initial drug-induced improvement in glycemic control deteriorates overtime requiring the use of additional antidiabetic drugs with different modes of action. Search for a new drug with a different mechanism of action brought the attention of scientists toward hypothalamic circadian neuroendocrinal rhythm associated with seasonal changes in migratory birds and vertebrate. Both migrating birds and vertebrate develop obesity and insulin resistance during hibernation, migration, and harsh winters when food availability is very low. The body fat stores and insulin action is controlled by the temporal interaction of circadian neuroendocrine oscillations, with reduced dopaminergic and enhanced serotonergic activities believed to be responsible for the obese insulin resistance phenotype. These changes occur in suprachiasmatic and ventromedial nuclei of hypothalamus. During transition to this obese state, insulin resistance of muscle and adipose tissue hampers glucose uptake in these tissues associated with a rise in hepatic glucose production and gluconeogenesis, leaving glucose for use by the brain. At the end of the season, animals revert to the insulin sensitive glucose-tolerant phase and become lean. This results in improved survival in times of food scarcity. The above changes in animals precisely mimic the changes observed in people with T2DM and the insulin-resistance syndrome. Bromocriptine mesylate is a quick release formulation of bromocriptine. Given in morning time, it increases dopaminergic tone resulting in reduced insulin resistance and improved glucose tolerance.[3]

The need for novel antidiabetic drugs lead investigators from the conventional "triumvirate" to "ominous octet" which implicated brain as the key player in glycemic control through neurohumoral mechanisms.[4] Bromocriptine mesylate is one such drug that upregulates hypothalamic dopaminergic tone reducing insulin resistance and improving glucose tolerance.[5]

There is Indian clinical study of using low dose bromocriptine as monotherapy and add-on therapy to metformin in type 2 diabetes.[6] The present study was undertaken to evaluate the efficacy of bromocriptine mesylate in maximal recommended dose as an add-on therapy to two oral antidiabetic drugs.

Objectives

To study the efficacy of bromocriptine mesylate as an add-on therapy in patients with T2DM inadequately controlled on two oral antidiabetic drugs.

MATERIALS AND METHODS

This was a prospective, non-randomized study conducted at Diabetes Clinic of PGIMS, Rohtak, India, after obtaining approval from Institutional Ethics Committee.

After taking informed consent, 50 patients of either sex, aged between 18 and 60 years with uncontrolled T2DM with glycosylated hemoglobin (HbA1c) between 7.5% and < 10% were included. All patients were on stable dosage of two antidiabetic drugs for ≥ 3 months which included metformin sulfonylurea combination in 42 subjects, and metformin vildagliptin combination in 8 subjects. Patients with type 1 diabetes, T2DM on insulin therapy, pregnant women, and patients with comorbid conditions were excluded.

Detailed history, physical examination, anthropometry, and biochemical parameters were recorded on a predesigned patient performa.

Bromocriptine mesylate was started as one tablet (0.8 mg) orally daily at 8 am with food and increased by one tablet per week until a maximum recommended daily dose of six tablets (4.8 mg/day) or until the maximum tolerated dose was achieved. This dose up-titration was done to avoid postural hypotension. The dosage of other two oral antidiabetic drugs remained stable during the study period.

All patients were followed up in clinic at 6 and 12 weeks. Efficacy of bromocriptine mesylate was assessed by measuring FBS (mg/dL), PPBS (mg/dL) and HbA1c (%) at 0, 6 and 12 weeks. Blood sugar levels were measured by standardized analyzers. HbA1c was estimated by latex agglutination inhibition assay method using an auto analyser.[7]

On each visit, patients were assessed for compliance using pill count method and drug side effects. At the end of the study, mean ± standard deviation (SD) values were compared using the paired Student's *t*-test. Statistical significance was defined as $P \leq 0.05$. Statistical analysis was performed using SPSS 17 statistical software.

RESULTS

The study included an equal number of male and female patients with mean ± SD of diabetes duration being 4.74 ± 3.89 years. The mean ± SD of age was 54.84 ± 8.36 years with a range of 34-68 years

The baseline mean ± SD FBS, PPBS, and HbA1c values were 146.86 ± 15.54 mg/dL, 227.92 ± 41.12 mg/dL and 8.66% ± 0.71%, respectively (Table 1). After 6 weeks of bromocriptine mesylate add-on therapy, FBS, PPBS, and HbA1c showed a mean change of −19.96 mg/dL, −45.90 mg/dL, and −0.85%, respectively, which were found to be statistically significant

($P < 0.05$) (Table 1). After 12 weeks of add-on therapy, FBS, PPBS, and HbA1c showed a mean change of −34.24 mg/dL, −60.36 mg/dL and −1.56%, respectively. When compared with baseline values, these were found to be statistically significant ($P < 0.05$) (Table 2).

Patients were grouped into poor control (HbA1c > 9%), fair control (HbA1c 8-8.9%), and good control (HbA1c 7.5-7.9%) as per their baseline HbA1c levels.[8] None of the patient was in excellent control (HbA1c < 7%), because we included the patients with HbA1c ≥ 7.5%. Patients with poor and fair baseline glycemic status (mean ± SD HbA1c 9.49 ± 0.22% and 8.51 ± 0.24%, respectively) achieved good glycemic control at 12 weeks (mean ± SD HbA1c 7.28 ± 0.41% and 7.13 ± 0.40%, respectively). Patients with good baseline glycemic status (mean ± SD HbA1c 7.69 ± 0.16%) achieved excellent glycemic control at 12 weeks (mean ± SD HbA1c 6.76 ± 0.36%). Mean change in HbA1c at 12 weeks was −2.21% and −1.38% in patients with poor and fair baseline glycemic status, respectively. Mean change at 12 weeks in patients with good baseline glycemic status was −0.93% (Table 3).

Five patients reported nausea, one headache, and one fatigue. Hypoglycemia was not reported in any patient.

DISCUSSION

T2DM is a chronic metabolic disorder characterized by insulin resistance, impaired beta cell function and multiple other metabolic/endocrinal abnormalities. At the time of the diagnosis, beta cell function has already been reduced by approximately 50% and further decreases at a rate of about 6% per year.[9] Because of its multifactorial pathogenesis and progressive nature, restoration of normoglycemia is difficult to achieve and requires multiple antidiabetic drugs in additive manner with different mechanism of action.[10] After a successful initial response to oral therapy, patients fail to maintain target HbA1c levels <7% at a rate of 5-10% per year. Hence, patients who were initially treated as monotherapy would eventually need second and possibly third antidiabetic drug of a different class and mechanism. In fact, the add-on therapy with third drug is needed when two drugs are not able to bring down HbA1c <7% even after 3 months.[11] We included diabetics with HbA1c values between 7.5% and ≤10% who failed to achieve glycemic control with two oral antidiabetic drugs for ≥3 months; hence a third antidiabetic agent was desirable in our patients. The baseline mean ± SD of FBS, PPBS, and HbA1c values of 146.86 ± 15.54mg/dL, 227.92 ± 41.12 mg/dL, and 8.66% ± 0.71%, respectively, suggested uncontrolled status of patients. After 6 weeks of bromocriptine add-on therapy,

Table 1: Mean change in parameters of glycemic control after 6 weeks of bromocriptine mesylate add-on therapy

Parameters	Mean±SD (range)		Mean change	Statistical significance
	At 0 week (baseline)	At 6 weeks		
FBS (mg/dL)	146.86±15.54 (106-172)	126.90±16.16 (86-156)	−19.96	Significant (P<0.001)
PPBS (mg/dL)	227.92±41.12 (136-302)	182.02±26.71 (130-268)	−45.90	Significant (P<0.001)
HbA1c (%)	8.66±0.71 (7.5-9.8)	7.81±0.58 (6.8-9.2)	−0.85	Significant (P<0.001)

SD: Standard deviation, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Glycosylated hemoglobin

Table 2: Mean change in parameters of glycemic control after 12 weeks of bromocriptine mesylate add-on therapy

Parameters	Mean±SD (range)		Mean change	Statistical significance
	At 0 week (baseline)	At 12 weeks		
FBS (mg/dL)	146.86±15.54 (106-172)	112.62±19.38 (85-163)	−34.24	Significant (P<0.001)
PPBS (mg/dL)	227.92±41.12 (136-302)	167.56±30.48 (106-224)	−60.36	Significant (P<0.001)
HbA1c (%)	8.66±0.71 (7.5-9.8)	7.10±0.43 (6.2-8.1)	−1.56	Significant (P<0.001)

SD: Standard deviation, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, HbA1c: Glycosylated hemoglobin

Table 3: Mean change in glycemic status at 12 weeks

Baseline status of glycemia (HbA1c)	Number of cases	Mean±SD (range)		Mean change	Statistical significance
		At 0 week	At 12 weeks		
≥9.0% (poor control)	17	9.49±0.22 (9.0-9.8)	7.28±0.41 (6.6-8.1)	−2.21	Significant (P<0.001)
8.0-8.9% (fair control)	22	8.51±0.24 (8.1-8.8)	7.13±0.40 (6.5-8.1)	−1.38	Significant (P<0.001)
7.5-7.9% (good control)	11	7.69±0.16 (7.5-7.9)	6.76±0.36 (6.2-7.6)	−0.93	Significant (P<0.001)
Total	50	8.66±0.71 (7.5-9.8)	7.10±0.43 (6.2-8.1)	−1.56	Significant (P<0.001)

SD: Standard deviation, HbA1c: Glycosylated hemoglobin

FBS, PPBS, and HbA1c showed statistically significant reduction ($P < 0.05$). All 50 patients were continued on bromocriptine mesylate add-on therapy until 12 weeks with further significant reduction in all three parameters ($P < 0.05$). The overall reduction in HbA1c in our study at 12 weeks was 1.56%. Reduction in HbA1c was more in diabetics with poor baseline glycemic control compared to those having fair and good control. Maximal dose of 4.8 mg/day was tolerated well by 43 patients. In seven patients, dose reduction was required due to side effects nausea, headache and fatigue.

Comparing with four other published studies of bromocriptine in T2DM, study duration of 12 weeks was similar to Ramteke et al. but shorter than 24 weeks study K, study L and 52 weeks safety trial.[3,6] Number of patients in our study was lesser than other four studies. Dosage of bromocriptine used in the study conducted by Ramteke et al. was fixed dose of 2.4 mg/day. Our study had more flexible dose pattern with dosages reaching optimal level of 4.8 mg similar to study K, study L and as in safety trial. Bromocriptine mesylate was used as add-on therapy to two antidiabetic agents in our study similar to safety trial. In other three studies, it was used as add-on to single antidiabetic agent. Although there were significant decrease in markers of short term glycemic control like FBS and PPBS, it is the long-term glycemic control measured by HbA1c which is most important. Decrease in HbA1c levels at 12 weeks (−1.56%) were maximum in our study compared to Ramteke et al. (−0.74%), study L (−0.4%), and study K (−0.1%). Significant fall in HbA1c in our study demonstrates long-term glycemic efficacy of bromocriptine mesylate.

Very few studies have been carried out to evaluate efficacy of bromocriptine mesylate in T2DM. Our study followed uncontrolled T2DM patients for a time period of 12 weeks which is sufficient enough to show the changes in HbA1c. We administered quick release formulation of bromocriptine which has better safety profile and was very well tolerated in patients. It is not associated with worrisome side effects like hypoglycemia. Dosage in our study had flexible dose pattern with dosages reaching the optimal level of 4.8 mg/day. Bromocriptine mesylate was found effective as add-on therapy on parameters of both short- and long-term glycemic controls. Decrease in HbA1c in our study was maximum among all the studies mentioned. Less number of patients and comparatively shorter study duration were the limitations of our study.

CONCLUSION

Bromocriptine mesylate is a novel agent with unique mechanism of action and is effective antidiabetic drug which when added on to existing oral antidiabetic therapy in uncontrolled diabetes helps achieve optimal glycemic control without any significant adverse effects. Hence it can be concluded that bromocriptine mesylate is a safe combinational antidiabetic agent. Studies of bromocriptine mesylate involving larger number of patients with longer study duration with additional testing parameters would be required to further study its strengths and limitations.

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How to cite this article: Garg KK, Chugh SN. Efficacy of bromocriptine mesylate as add-on oral antidiabetic agent in type 2 diabetes mellitus. Int J Med Sci Public Health 2017;6(6):992-995.

Source of Support: Nil, **Conflict of Interest:** None declared.