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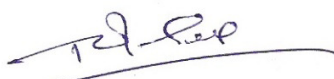
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Controlled clinical study of an Ayurvedic anti diabetic formulation (*BGR-34*) for its efficacy and safety in patients with type 2 Diabetes mellitus

Report By :-

Principle Investigator & Correspondent	- Dr. B.P. Gupta, Medical Superintendent
Co-Investigators	- Dr. Aarti kumar, Physician Dr. Bhanu Pratap Singh Tomar, Physician
Venue	- Aggarwal hospital, 24/9 Shakti Nagar, Delhi - 110007
No. of patients	- 56
Duration	- 4 months (2014-15)
Conclusion	- As per enclosure


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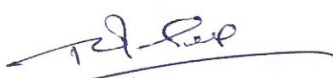
Controlled clinical study of an Ayurvedic anti diabetic formulation BGR-34 Tablets for its efficacy and safety in patients with Diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a common and very much prevalent metabolic disorder affecting the citizens of both developed and developing countries. It is estimated that 7.1% of the adult Indian population is affected by this disorder. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin. Despite considerable progress in the management of T2DM by oral hypoglycemic agents, search for newer drugs continues, since the existing synthetic drugs have several limitations. A number of herbal drugs have been acclaimed for their anti-diabetic properties in the traditional systems of medicine. Presently, alternative interventions are being looked for, from herbal drugs, which may provide effective control of hyperglycemia. The other added advantages of these herbal drugs/therapies are that these drugs are useful in delaying/preventing the onset of complications associated with type 2 diabetes mellitus. BGR-34 is a herbal/Ayurvedic formulation comprising of promising anti-diabetic herbs, well described in Ayurvedic texts (Table 1). In pre-clinical studies, BGR-34 has been reported to significantly reduce high blood sugar level in diabetes induced experimental subjects. BGR-34 was further found to improve LFT's, KFT's, and Lipid profile significantly and provide pronounced anti-oxidant activity.

Table 1. Components used in formulation of BGR-34

Components (herbs)	Descriptive role
<i>Trigonella foenum-graecum</i>	Delays absorption of glucose from GIT.
<i>Gymnema sylvestre</i>	Increases the activity of enzymes responsible for glucose uptake and utilization and prevents inhibition of peripheral utilization of glucose by somatotropins and corticotropin.
<i>Tinospora cordifolia</i>	Preventive role on the oxidative stress in Diabetes mellitus: acts as lipid metabolic regulator & immunomodulator.
<i>Berberis aristata</i>	Promotes functional recovery of β - cells.
<i>Rubia cordifolia</i>	Inhibits Advanced glycation end products (AGEs) accumulation in diabetic nephropathy
<i>Pterocarpus marsupium</i>	Possesses insulin like molecules and acts as pancreas toner by intensive metabolic regulation in diabetes. It is also found to be insulinogenic, enhancing insulin release and conversion of pro-insulin to insulin


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Aim & Objectives

To study the efficacy and safety of Ayurvedic formulation, BGR-34, on blood glucose regulation/management in patients with mild to moderate type 2 diabetes mellitus.

Methodology


A double blind placebo controlled clinical study of BGR-34 (tablets) in patients with mild to moderate type 2 diabetes mellitus was approved by the independent human ethics committee of Aggarwal Hospital, New Delhi (India). 140 patients from the OPD at Aggarwal Hospital were screened, out of which 64 patients were selected after applying inclusion and exclusion criteria.

Inclusion Criteria:

- ✓ Age: 25 to 60 years
- ✓ Patients with type 2 Diabetes mellitus
- ✓ Fasting blood glucose >126 mg/dL
- ✓ Absence of any other significant disease or clinically significant medical history on physical examination during screening in the view of the investigator.
- ✓ Subjects willing to provide written informed consent to participate in the study.

Exclusion Criteria:

- ✓ Patients on Insulin
- ✓ Patients with acute infections or chronic debilitating diseases, tuberculosis, malignancy, HIV infection etc.
- ✓ Any life threatening serious disorder of the liver, kidneys, heart, lungs or other organs
- ✓ Pregnancy and lactation
- ✓ Patients diagnosed with severe end organ damage
- ✓ Unwillingness to give written informed consent for participation in the study.


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Study design


A double blind placebo controlled parallel design was used to compare the effect of an Ayurvedic drug (BGR-34; drug group) vs. Placebo (control group; table 2) over a period of 16 weeks, after a run-in period of 4 weeks among patients with mild to moderate type 2 diabetes mellitus. The study was approved by independent human ethics committee of Aggarwal Hospital, New Delhi (India). Similar dietary and exercise counseling was given to all the participants and were instructed to maintain the same level of physical activity throughout the study. Participants met with the investigators once in 4 weeks for clinical evaluation and to provide updates on drug, diet and lifestyle compliance (Figure 1).

Table 2. Composition of Placebo

Placebo	Composition
Triphla (250 mg tablets)	<i>Emblica officinalis</i> (Amla)
	<i>Terminalia belerica</i> (Bahera)
	<i>Terminalia chebula</i> (Haritaki)

A total of 140 patients were screened from the outpatient department (OPD) of Aggarwal Hospital, Delhi (India), out of which 64 patients were recruited in the study after applying inclusion and exclusion criteria. Within 1st week of initiation 3 patients withdrew their consent from placebo group due to reasons not associated with study [pregnancy (n=1), hectic work schedule (n=2)] and 1 patients withdrew consent from drug group (shift based job). 3 patients (2 drug group and 1 placebo group) were lost to follow up and one patient from drug group was dropped due to poor compliance. A total of 56 patients (28 drug group and 28 placebo group) completed the study (Figure 1).

Prior to initiation of the study, written informed consent was obtained from each patient. The clinical study was conducted for 16 weeks. At the base line, blood glucose – fasting and post prandial, glycosylated hemoglobin, test were done. Patients were randomized into placebo and drug arms for 16 weeks (after 4 weeks of run in period). Patients were provided with medicine, either drug/placebo coded with particular number from 1 to 64 and advised to take 2 tablets of the drug/placebo twice a day as adjuvant along with prescribed anti diabetic drugs under existing treatment if any. The patients were investigated after every 4 weeks for fasting and post prandial blood glucose. Further, the patients were advised to seek medical advice and report immediately in case of development of any complications or any untoward events at any stage during the course of the study. At study completion (after 16 weeks of the treatment), blood glucose-fasting and post prandial, glycosylated hemoglobin, were repeated.


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Assessment Method

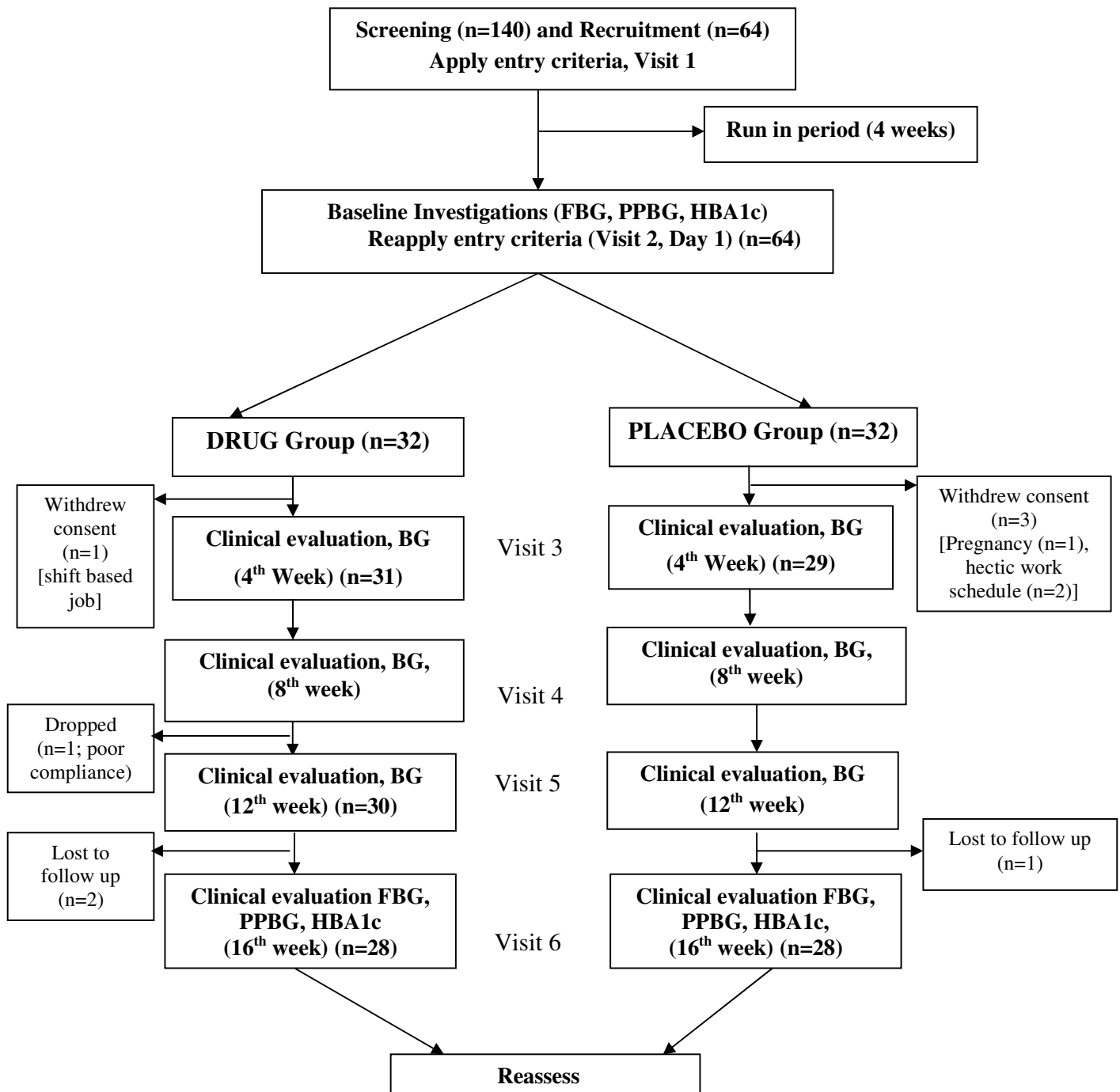


Figure 1. Study design and patient recruitment process

BG; Blood glucose, FBG; Fasting blood glucose, PPBG; Post prandial blood glucose, HBA1c; Glycosylated haemoglobin

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Statistical Analysis

Data was arranged in MS Excel. Student's t test was used to compare difference in mean values between the two groups. Chi-square test was used for categorical variables. Paired t-test has been used for within group analysis. For every outcome variable, results are presented as mean \pm sd (standard deviation), p value <0.05 was considered statistically significant. STATA 12.0 (STATA Corp, Houston, TX, USA) statistical software has been used for data analysis.

Observations & Results

56 patients (30 male and 26 females) with type 2 diabetes mellitus completed the study. There were 28 patients in the BGR-34 group (drug arm) and 28 patients in the placebo group (placebo arm). The mean age of patients for BGR-34 and placebo group were 47.9 ± 6.7 years and 49.7 ± 5.9 years respectively. Average body weight in BGR-34 group was 67.04 ± 8.6 kg and in placebo group it was 70.1 ± 6.9 kg (Table 3). The difference in Age, body weight & number of patients in the drug and placebo group was not found to be significant.

Table 3. Demographic profile of patients according to treatment group

Variables	Drug Group	Placebo	p value [†]
	(n=28)	(n=28)	
	(mean \pm sd)	(mean \pm sd)	
Age (years)	47.9 ± 6.7	49.7 ± 5.9	0.318
Weight (kg)	67.04 ± 8.6	70.1 ± 6.9	0.1444
Males (%)	16 (57.1)	14 (50.0)	0.592 [#]
Females (%)	12 (42.9)	14 (50.0)	

[†] Student's t-test, [#] Chi square test

Fasting Blood Glucose (FBG)

Biochemical results of all patients were analyzed before and after completion of the study. Blood sugar fasting showed significant reduction ($p=0.0016$) from 196.0 ± 32.7 mg/dL to 129.3 ± 33.3 mg/dL in BGR-34 treated group as compared to placebo group where fasting blood sugar reduced from 187.2 ± 43.3 mg/dL to 162.9 ± 41.6 mg/dL. The percent reduction in the BGR-34 treated group was highly significant ($p<0.001$) as compared to the placebo group (Table 4).

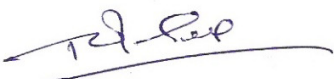

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Table 4. Effect of BGR-34 and Placebo on Fasting Blood Glucose (FBG) mg/dL on completion of study as compared to that at base line

Variables	Drug Group	Placebo	Difference (95% CI)	p value ‡
	(n=28)	(n=28)		
	(mean ± sd)	(mean ± sd)		
FBG (mg/dL)				
Baseline	196.0 ± 32.7	187.2 ± 43.3	8.8 (-11.7 to 29.3)	0.3939
Post intervention	129.3 ± 33.3	162.9 ± 41.59	-33.5 (-53.7 to -13.3)	0.0016
Change (reduction)	66.7 ± 23.2	24.4 ± 14.3	42.3 (31.9 to 52.6)	<0.001
% Change (% reduction)	34.3 ± 10.7	13.2 ± 7.7	21.2 (6.1 to 26.2)	<0.001

‡ Student's t test; FBG-fasting blood glucose

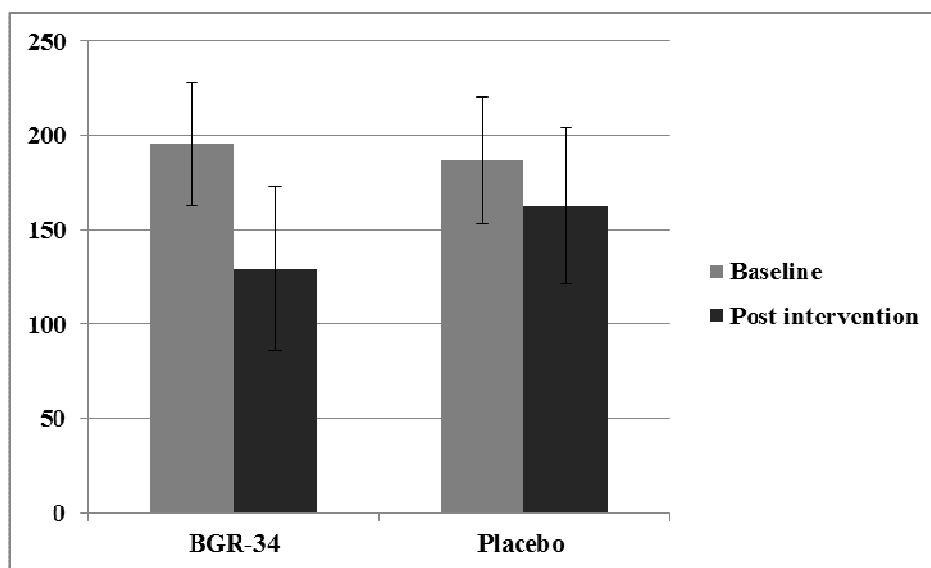


Figure 2. Comparison between means (± sd) of Fasting Blood Glucose (FBG) mg/dL values in drug and placebo arms before and after the treatment

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Post Prandial Blood Glucose (PPBG)

Blood sugar post prandial showed significant reduction ($p < 0.001$) from 276.8 ± 59.7 mg/dL to 191.9 ± 49.3 mg/dL in BGR-34 treated group as compared to placebo group where post prandial blood sugar reduced from 294.9 ± 56.3 mg/dL to 262.6 ± 52.9 mg/dL. The percentage reduction in the BGR-34 treated group was highly significant ($p < 0.001$) as compared to the placebo group (Table 5).

Table 5. Effect of BGR-34 and Placebo on Post Prandial Blood Glucose (PPBG) mg/dL at baseline and after completion of the study

Variables	Drug Group	Placebo	Difference (95% CI)	p value ‡
	(n=28)	(n=28)		
	(mean \pm sd)	(mean \pm sd)		
PPBG (mg/dL)				
Baseline	276.8 ± 59.7	294.9 ± 56.3	-18.1 (-49.2 to 12.9)	0.2482
Post intervention	191.9 ± 49.3	262.6 ± 52.9	-70.7 (-98.1 to -43.3)	<0.001
Change (reduction)	84.8 ± 36.3	32.2 ± 18.4	52.6 (37.2 to 68.0)	< 0.001
% Change (% reduction)	30.5 ± 10.6	10.9 ± 5.9	19.6 (14.9 to 24.2)	< 0.001

‡ Student's t test; PPBG-post prandial blood glucose

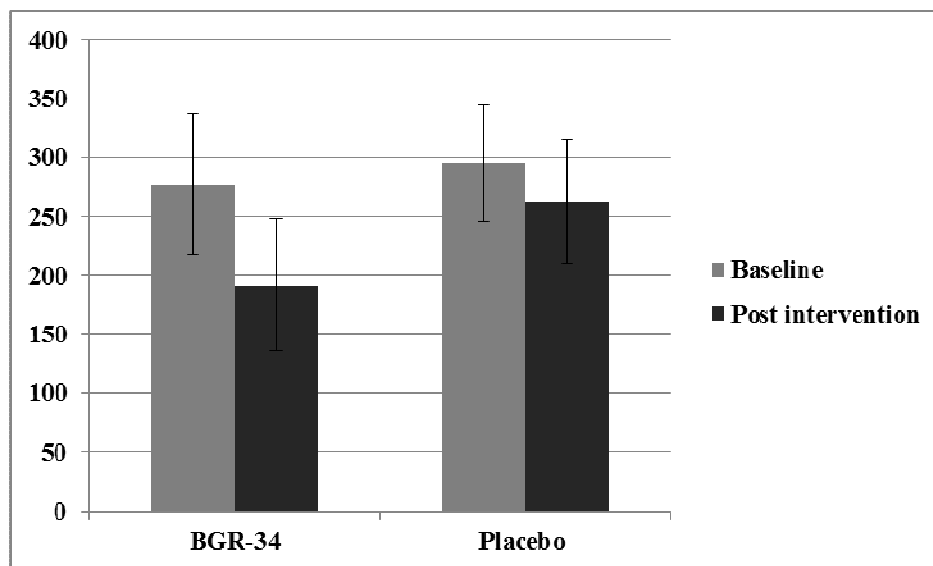


Figure 3. Comparison between means (\pm sd) of Post Prandial Blood Glucose (PPBG) mg/dL values in drug and placebo arms before and after the treatment

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Glycosylated haemoglobin

Glycosylated haemoglobin decreased from 9.56 ± 1.15 to 7.58 ± 0.99 which was found to be a highly significant decline in the BGR-34 group ($p=0.001$). On the other hand in the placebo group there was relatively a lesser reduction in the glycosylated haemoglobin level from 9.91 ± 1.05 to 8.86 ± 1.30 during the 16 week study period (Table 6).

Table 6. Effect of BGR-34 and Placebo on Glycosylated Haemoglobin (HbA1c) after completion of the study as compared to base line

HbA1c	Drug Group	Placebo	Difference (95% CI)	p value ‡
	(n=28)	(n=28)		
	(mean \pm sd)	(mean \pm sd)		
Baseline	9.56 ± 1.15	9.91 ± 1.05	-0.35 (-0.94 to 0.25)	0.2469
Post intervention	7.58 ± 0.99	8.86 ± 1.30	-1.28 (-1.90 to -0.66)	0.001
Change (reduction)	1.98 ± 1.02	1.05 ± 0.52	0.93 (0.49 to 1.36)	0.001
% Change (% reduction)	20.31 ± 9.3	10.87 ± 5.94	9.45 (5.26 to 13.63)	< 0.001

‡ Student's t-test

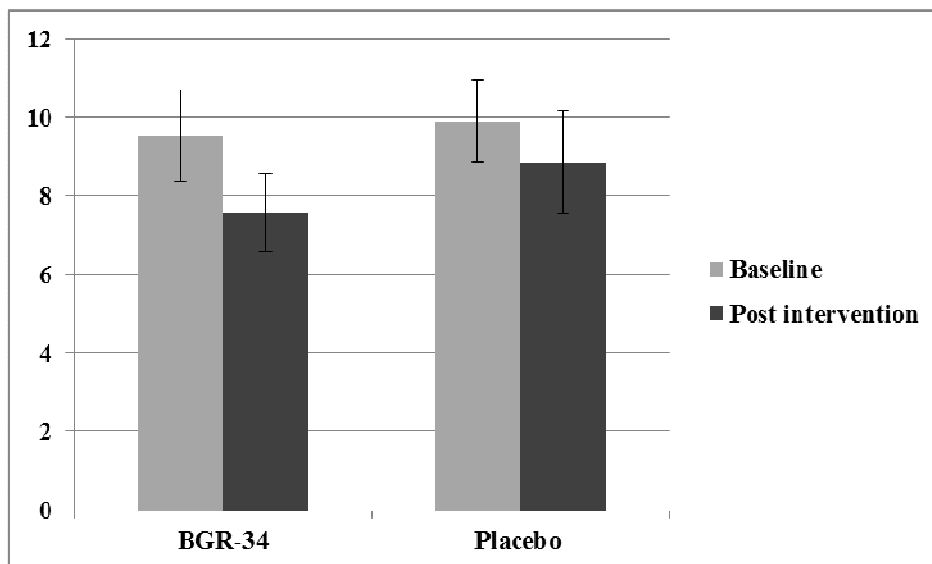
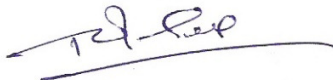


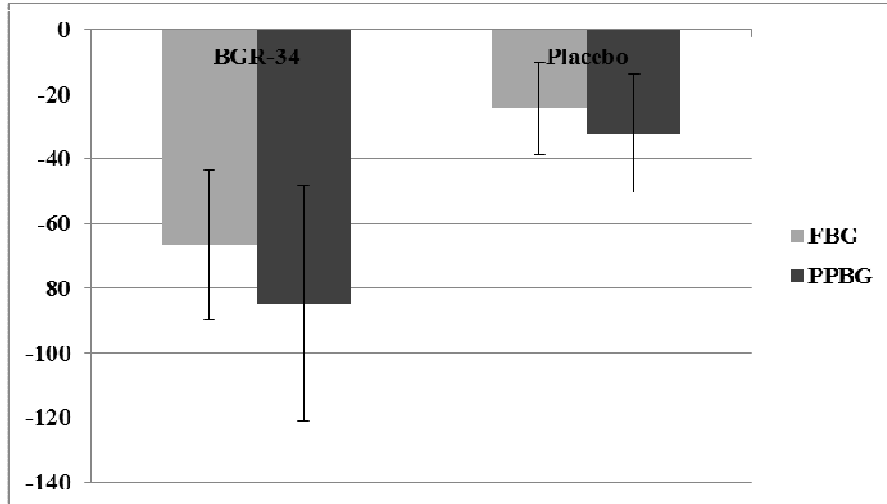
Figure 4. Comparison between means (\pm sd) of Glycosylated Haemoglobin (HbA1c) values in drug and placebo arms before and after the treatment


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Reduction

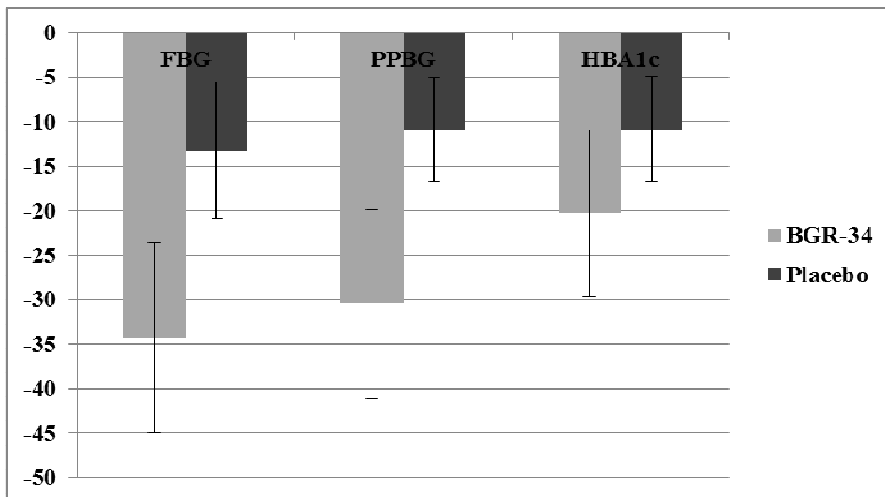
Both the groups showed reduction in fasting and post prandial blood glucose, however, BGR-34 group demonstrated significant improvements in the status of the patient with significantly higher reductions (and percentage reductions; Table 4 and 5; Figure 5 and 6). Statistical analysis revealed that the percentage reduction in the BGR-34 treated group on fasting blood glucose was more than that on post prandial blood glucose.

Figure 5. Change (reduction) in blood glucose levels between the two groups



Values represent mean reduction (change) \pm sd. FBG-fasting blood glucose; PPBG-post prandial blood glucose

Figure 6. Percent change (reduction) in blood glucose levels between the two groups



Values represent mean percent reduction (% change) \pm sd. FBG-fasting blood glucose; PPBG-post prandial blood glucose; HbA1c-glycosylated hemoglobin.

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No untoward effects were observed in any of the patients on BGR-34. Rather patients reported improvement in quality of life along with relief in symptoms like polyuria, polyphagia, polydipsia, general fatigue, pain in calf muscles, burning sensation of soles and palms, dryness of mouth, itching genitals, decreased libido, blurred vision, delayed healing of wounds and overall improvement in feeling of wellbeing. Improvement in appetite and digestion with no gastric discomforts were also reported in BGR-34 group.

Conclusion


BGR-34 showed very promising results with respect to glycemic parameters in patients with type 2 diabetes mellitus. There was a significant improvement in the feeling of wellbeing due to better control of hyperglycemia. The various mechanism through which the drug showed these results may be attributed to i) delays in absorption of glucose from GIT, ii) inhibition of Advanced glycation end products (AGEs) accumulation and iii) enhancing insulin release and conversion of pro-insulin to insulin. It is further suggested that BGR-34 should be further extensively used as a mono therapy/adjunctive therapy for the regulation/ management / control of blood glucose level.

Adverse events

No adverse events were reported (or occurred) during the course of study.

Acknowledgement

We are thankful to all the participants of the study for their co-operation and also to Aimil Pharmaceuticals (I) Ltd. for providing us the required drug and placebo samples.



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