ORIGINAL ARTICLE

EFFECT OF COMBINATION OF NIGELLA SATIVA AND TRIGONELLA FOENUM-GRAECUM SEEDS WITH GLIBENCLAMIDE ON BLOOD SUGAR LEVELS IN TYPE-2 DIABETES MELLITUS PATIENTS

Ashfaque Rahim Memon, Abdul Rahim Memon, Shaheen Sharaf Shah, Fatehuddin Khand, Imran Ali Shaikh

ABSTRACT

OBJECTIVE: To evaluate the effect of combination of Nigella sativa and Trigonella foenum-graecum seeds with Glibenclamide on blood sugar levels in type-2 diabetes mellitus patients.

DESIGN: A randomized clinical trial

PLACE AND DURATION OF STUDY: Diabetic outpatient clinics of Isra University Hyderabad and Liaquat University of Medical and Health Sciences Jamshoro, Pakistan from March to August 2008.

PATIENTS AND METHODS: For this study, Type-2 diabetic mellitus patients on Glibenclamide, who gave written consent to volunteer in the study, were randomly divided into two groups. Fifty patients in Group “A” (Control Group) remained on routine dose of Glibenclamide, while fifty patients in Group “B” (Intervention Group) were kept on a capsule containing combined powder of N-sativa & T. foenum-graecum seeds powder, in addition to their routine dose of Glibenclamide. Patients in both the groups were evaluated for a period of 3 months for fasting and random sugar levels.

RESULTS: It was found that the blood sugar level fasting (p-value=0.003) and the random (p-value=0.001) significantly decreased in intervention group compared to control group.

CONCLUSION: This study indicates that combination therapy of N. sativa and T. foenum-graecum seeds with Glibenclamide has significant effect in controlling hyperglycemia.

KEYWORDS: N. sativa and T. foenum-graecum, Glibenclamide, Hyperglycemia, Type-2 diabetic patients.

INTRODUCTION

Type-2 Diabetes Mellitus accounts for 90-95% of diabetic cases. Its incidence has increased in children and adolescents in developed countries during the past decade. Genetic factors are agreed to be more important in type-2 diabetes than in type-1 diabetes. Two metabolic defects that characterize type-2 diabetes mellitus are a derangement in Beta-cell secretion of insulin and inability of peripheral tissues to respond to insulin. However, the etiology of these defects and the details of their interplay in the pathogenesis of type-2 diabetes mellitus remain unclear. The beneficial effects of modern medicine on glycemic levels are well documented. The preventing activity of these allopathic drugs against progressive nature of diabetes and its complications is modest and not always effective. Oral antidiabetic agents like sulfonylureas, biguanides and other groups used for the treatment of type-2 diabetes, have many side effects. Sulfonylureas for example are associated with hypoglycemia, biguanides with lactic acidosis and thiazolidinediones with risk of myocardial infarction and heart failure. In addition to that, majority of the type-2 diabetic patients do not achieve target glycemic levels with above therapies and hence need insulin therapy. Insulin therapy although gives effective glycemic control, yet its demerits which include ineffectiveness through an oral administration, requirement of constant refrigeration of the drug and hypoglycemia in the event of excess dosage limits its use. In views of above problems, the popularity of complementary medicine has increased. Surveys conducted in Australia and United States of America indicate that almost 48.5% and 34% respondents respectively had used at least one form of unconventional therapy including herbal medicine. According to world health organization (WHO), about three-quarters of the world population rely upon traditional remedies (mainly herbs) to cure different ailments as these have relatively fewer side effects. More than 1200 different plants have been described as traditional treatment for diabetes. Some of these plants have also been pharmacologically tested and shown to be

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of some value in diabetes. Nigella sativa and Trigonella foenum-graecum are two important examples in this group. N. sativa is widely grown in different parts of the world. In South Asia, it is known as Kalonji and in western world as Black cumin. It belongs to family Ranunculaceae and is traditionally used worldwide, especially in the Indian subcontinent and Arabian countries as a natural remedy for a number of illnesses and conditions that include asthma, hypertension, diabetes, inflammation, cough, bronchitis, headache, eczema, fever, dizziness and influenza. Owing to saying of Prophet Muhammad (S.A.W.S) that this plant is full of medicinal value, the popularity of this plant had been highly enhanced.

Trigonella foenum-graecum (known as Helba in Arabic and fenugreek in English) is traditionally known to induce hypoglycemia. The activity of seeds and leaves of this plant have been investigated and found to exhibit a hypoglycaemic effect in animals and in human beings. The aim of the present study was to evaluate the effect of the combination of N. sativa and T. foenum-graecum seeds with Glibenclamide in type-2 diabetes mellitus patients. Glibenclamide is generally used as a reference drug in anti-diabetic activity test.

**PATIENTS AND METHODS**

This clinical trial was conducted in the Diabetic outpatient clinics of Isra University Hyderabad and Liaquat University of Medical and Health Sciences Jamshoro, from March to August 2008.

**Inclusion Criteria:** All type-2 diabetes mellitus patients on Glibenclamide with Fasting blood sugar level more than 131mg/dl and HbA1c more than 7% were included in the study.

**Exclusion Criteria:** Followings were excluded from study:
- Patients with any other endocrine dysfunction
- Pregnant or lactating women
- Hypertensive patients
- Patients on steroid therapy.

**Study population:** One hundred type-2 diabetes mellitus patients who fulfilled the inclusion and exclusion criteria were included in the study. All the patients were advised to take their usual meal and maintain their daily routine. Ethics review committee/institutional review board approval was obtained for the study. Written informed consent was obtained from all patients before start of trial. Selected patients were randomly divided into two groups.

**Group A (Control):** This group comprised of fifty type-2 diabetic patients on Glibenclamide treatment only.

**Group B (Intervention Group):** This group comprised of fifty type-2 diabetic patients kept on capsules, containing combined powder of Nigella sativa and Trigonella foenum-graecum seeds, in addition to their routine dose of Glibenclamide.

**Period of study:** Each patient from both the groups was treated for a period of 3 months.

**Preparation of Drugs:** One tablet of Glibenclamide (Daonil) composed of 5 mg of Glibenclamide. One herbal capsule used in intervention group contained powder of combination of crushed N. sativa seeds (250 mg) and T. foenum-graecum seeds (250 mg). Authentic seeds of N. sativa and T. foenum-graecum were purchased from local market and identified and confirmed by department of Botany University of Sindh Jamshoro. Seeds, after cleaning and shade drying were grounded in a mechanical grinder and passed through 80 mesh sieve. Powder obtained in each case was kept separately in a glass jar so that it dried completely. The dried powders were then filled in capsules in equal amounts i.e. 250 mg for each of N. sativa and T. foenum-graecum.

According to fasting blood sugar (FBS) levels, doses prescribed to patients in Group A and B are depicted in Table I.

**Blood Sugar level determination:** Blood sugar level was spectrophotometrically measured in blood sample drawn after overnight fast for fasting blood sugar level and 2 hours after breakfast for random blood sugar level. Blood sugar level was estimated three times per week (two fasting and one random sample) for first week, then once a week i.e. fasting in one week and random for remaining weeks.

**Statistical Analysis:** In this study, as various parameters have been statistically compared for differences in mean values of fasting and random blood glucose level measured at many different intervals between groups, so statistical test “Repeated Measure ANOVA (Analysis of Variance)” using General Linear Model in SPSS was used. Since, blood sugar levels (fasting and random) were analyzed at four different time intervals, so according to rules of Repeated Measure ANOVA significant p-value i.e. <0.05 was divided by 4 (no of time intervals) to obtain level of significance for blood sugar levels, which came to be <0.012.
RESULTS

Demographic characteristics of patients of both the groups are depicted in Table II. Majority of the patients in both the groups were above 39 years of age and were female. There were no significant differences between groups for mean age and gender. In Table III, fasting blood sugar levels for A and B group patients at baseline and after one, two, and three months of treatment are depicted. Significant difference was observed in FBS levels within each group at different time intervals (p-value<0.001). No significant difference between the patients of two groups was observed in FBS levels at baseline (p-value=0.039) and after 1 month of treatment (p-value=0.316), but the difference was significant after 2 months (p-value=0.006) and 3 months (p-value=0.003) of treatment. After three months of treatment, FBS level decreased by 58.03 mg/dl in the intervention group, whereas no decrease was noted in the control group. Table IV presents random blood sugar levels in Group A and B patients. Significant difference was observed in random blood sugar levels within each group at different time intervals (p-value<0.001). No significant difference between the patients of two groups was observed in random sugar levels at baseline (p-value=0.021) and after 1 month of treatment (p-value=0.190), but the difference was significant after 2 months (p-value<0.001) and 3 months (p-value<0.001) of treatment (Figure 1). Moreover, the interaction of time and group was significant (p-value<0.001). This means, in group A patients, there was no variation in random blood glucose level, but in group B patients, random blood glucose level decreased with time.

TABLE I: DOSES PRESCRIBED TO GROUP A & B PATIENTS, ACCORDING TO THEIR FASTING BLOOD SUGAR LEVELS (FBS)

<table>
<thead>
<tr>
<th>FBS level (mg/dl)</th>
<th>Group A (Control)</th>
<th>Group B (Intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glibenclamide dose</td>
<td>Combined dose of <em>N. sativa</em> &amp; <em>Trig foenum-graecum</em> with Glibenclamide</td>
</tr>
<tr>
<td>131-150</td>
<td>5 mg (1 tablet)</td>
<td>5 mg + 1000 mg (2 capsules)</td>
</tr>
<tr>
<td>151-180</td>
<td>10 mg (2 tablet)</td>
<td>10 mg + 1000 mg (2 capsules)</td>
</tr>
<tr>
<td>181-200</td>
<td>15 mg (3 tablet)</td>
<td>15 mg + 1500 mg (3 capsules)</td>
</tr>
<tr>
<td>200-230</td>
<td>20 mg (4 tablet)</td>
<td>20 mg + 2000 mg (4 capsules)</td>
</tr>
<tr>
<td>231 or more</td>
<td>20 mg (4 tablet)</td>
<td>20 mg + 2000 mg (4 capsules)</td>
</tr>
</tbody>
</table>

1. One tablet of Glibenclamide contained 5 mg of Glibenclamide
2. One capsule of combined powder of *N. sativa* and *Trig foenum-graecum* contained 500 mg, 250 mg of each

TABLE II: DEMOGRAPHIC CHARACTERISTICS OF PATIENTS BY GROUP

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Age Group: &lt;30 years</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>30 - 39</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>40 &amp; above</td>
<td>51±1.36</td>
<td>48±1.50</td>
</tr>
<tr>
<td>Mean Age (S.E.M)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: Male</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>
TABLE III: FASTING BLOOD SUGAR LEVELS (MG/DL) IN GROUP A AND GROUP B PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Group A (Control) (Mean ± S.E.M)</th>
<th>Group B (Intervention) (Mean ± S.E.M)</th>
<th>*p-value between groups at different times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>178 ± 7.16</td>
<td>200 ± 7.68</td>
<td>0.039</td>
</tr>
<tr>
<td>After 1 month</td>
<td>174 ± 7.70</td>
<td>185 ± 7.73</td>
<td>0.316</td>
</tr>
<tr>
<td>After 2 months</td>
<td>180 ± 8.99</td>
<td>146 ± 7.49</td>
<td>0.006</td>
</tr>
<tr>
<td>After 3 months</td>
<td>177 ± 8.41</td>
<td>142 ± 7.65</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*p-value <0.012 was considered significant.

TABLE IV: RANDOM BLOOD SUGAR LEVELS (MG/DL) IN A AND B GROUP PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Group A (Control) (Mean ± S.E.M)</th>
<th>Group B (Intervention) (Mean ± S.E.M)</th>
<th>*p-value between groups at different times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>290 ± 7.83</td>
<td>318 ± 8.84</td>
<td>0.021</td>
</tr>
<tr>
<td>After 1 month</td>
<td>285 ± 8.52</td>
<td>271 ± 7.0</td>
<td>0.190</td>
</tr>
<tr>
<td>After 2 months</td>
<td>292 ± 8.53</td>
<td>233 ± 9.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 3 months</td>
<td>289 ± 8.70</td>
<td>224 ± 8.25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value<0.012 was considered significant

DISCUSSION

Pharmacological and clinical evaluations had indicated that herbal drugs have a mild, but significant, blood glucose lowering effect and that the long-term use of these may be advantageous over chemical drugs in alleviating some of the chronic diseases and complications caused by diabetes. Additionally, the use of these natural agents in conjunction with conventional drug treatments, such as a chemical agent or insulin, permits the use of lower doses of the drug and / or decreased frequency of administration which decreases the most commonly observed side effects. In this study, an attempt was made to investigate the antidiabetic efficacy of combination of two herbal drugs namely *Nigella sativa* and *Trigonella foenum-graecum* with Gilbenclamide on type-2 diabetic patients, who were already on Gilbenclamide. Patient volunteers selected for this study were randomly divided into two groups namely control group and intervention group. Control group consumed Tablet Gilbenclamide alone while intervention group was kept on capsules containing combined powder of *N-sativa* and *T. foenum-graecum* seeds, in addition to their routine dose of Gilbenclamide. Blood sugar levels fasting and random were monitored during the study period. Results of the present study showed that combination therapy significantly decreased fasting and random blood sugar levels after the treatment of 2 months and 3 months respectively.

Above effects on blood sugar level indicate significant but delayed response of combination of these two plants in reducing hyperglycemia. In other studies conducted previously, *N. sativa* had shown its effectiveness in reducing hyperglycemia when used alone or in combination with other herbal drugs. Similarly, *T-foenum-graecum* had shown its effectiveness in reducing hyperglycemia when used alone or in combination with other herbal drugs. In some previous studies, in which these plants were used alone, a higher dose of these plants was required for better control of blood sugar level. There are many herbal formulas, such as cogent db and others which have been investigated for the treatment of type-2 diabetes and these had shown better diabetic control with lesser side effects. The present study gives good support to these studies and suggests that combination therapies of plants can provide good diabetic control with minimal side effects. This study had few limitations such as limited sample size, convenient sampling technique (non-probability). Therefore, these findings shall be interpreted carefully.
CONCLUSION

From this study, it may be concluded that combination therapy of *N. sativa* and *T. foenum-graecum* with Gilbenclamide has significant but delayed beneficial effects in treating hyperglycemia in diabetic patients. So, like other herbal formulas this combination can be utilized in conjunction with conventional drug treatments to achieve better diabetic control.

REFERENCES


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