Topical Nigella Sativa product: A new candidate for the management of diabetic peripheral neuropathy

Seyed-Ali Khodaie  
Shahid Sadoughi University of Medical Sciences and Health Services

Haniyeh Nikkhah  
Shahid Sadoughi University of Medical Sciences and Health Services

Nasim Namiranian  
Shahid Sadoughi University of Medical Sciences and Health Services

Marzie Abotorabi  
Shahid Sadoughi University of Medical Sciences and Health Services

Maryam Askari  
Shahid Sadoughi University of Medical Sciences and Health Services

Saeed Hosein Khalilzadeh  
Shahid Sadoughi University of Medical Sciences and Health Services

Amidoddin khatibi Aghda  
Shahid Sadoughi University of Medical Sciences and Health Services

mohammad kamallnejad (✉ nadianikkhah@yahoo.com)  
Shahid Beheshtei University of Medical Sciences School of Pharmacy  
https://orcid.org/0000-0002-5946-4913

Research Article

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Abstract

Background: Diabetic neuropathy is one of the most common complications of diabetes. The synthetic drugs available in the market have side effects and limitations for diabetic patients, the vast majority of whom are in the upper age group. In this regard, based on Persian medicinal sources, Nigella Sativa (N. sativa) has proved to have beneficial effects on nerve-originated pain and neurological disorders. In this study, the effect of N. sativa is investigated topically in patients with diabetic neuropathy, and the results are compared with gabapentin capsules.

Method: This study was performed as a double-blind clinical trial on 120 neuropathic patients. The patients were divided into three groups. The first group received a topical N. sativa product as an ointment, the second group was given a topical placebo and the third received 300 mg gabapentin capsules. The blindness was done in first and second groups. The patients were evaluated for eight weeks using the Michigan Response Questionnaire.

Results: The data were elicited from the patients’ answers to a number of questions in the Michigan questionnaire. There were statistically significant differences between the group that received the topical N. sativa product and the other two groups in terms of legs and feet numbness (p-value = 0.00), burning pain in feet or legs (p-value = 0.00), muscle cramps in feet or legs (p-value = 0.00), prickling fleeing in feet or legs (p-value = 0.00), hurting of the skin when the bed covers touch it (p-value = .005), aggravated symptoms at night (p-value = 0.00) and hurting feelings in the legs when walking (p-value = .0327). However, the three studied groups were not statistically different in distinguishing hot water from cold water.

Conclusion: According to the results of this study, the topical use of N. sativa, compared to the current drugs, has acceptable improving effects on diabetic neuropathic patients.

1. Introduction

Diabetic neuropathy is one of the most common complications occurring in at least half of all diabetic patients. The most typical form of this disorder is distal symmetrical polyneuropathy (DSP) (1). The DSP complication not only creates psychological problems (2) and considerable disability by impacting the patient’s quality of life but also is one of the main predisposing factors for diabetic foot, including Charcot joint disease and foot ulcers (3). It also imposes a very high cost on the patient and the community (4, 5).

The proper control of blood sugar is one of the effective ways to prevent the complications of diabetes, including neuropathy. So far, many researchers have suggested synthetic and herbal medicines for the treatment of this disorder. Considering that most patients in this context are elderly and take multiple medications (6) and that conventional drugs generally have side effects and are not allowed in patients with liver and kidney problems (7, 8), the tendency to use herbal medicines as well as traditional and complementary medicines has recently become more common. Studies have shown that the proper use
of herbal medicines is associated with fewer side effects (9). Persian medicine is one of the rich schools of complementary medicine that can provide new treatment methods and drugs with the help of modern technologies (10). In Persian medicine sources, Khaddar is mentioned as a general name for a group of diseases that have similar sensory disturbance symptoms such as pain, paresthesia and numbness. From the perspective of some researchers, Khaddar is equivalent to sensory neuropathy (11). *N. sativa* is one of the medicinal plants that has been used by Persian medicine specialists orally, topically and olfactory to manage nerve-originated pains and neurological disorders (12, 13).

*N. sativa* (commonly known as black seed, black cumin or kalonji) is a member of the Ranunculaceae family. It is a source of oil whose main components are *p*-Cymene (37.3%) and thymoquinone (13.7%) (14). The plant has long been used to treat various diseases (15, 16). A number of studies have shown that it can improve metabolic factors in diabetes (17). It was found in a review study that consuming *N. sativa* in various forms can help diabetic patients. For these patients and those with glucose intolerance, *N. sativa* reduce appetite, intestinal glucose uptake, hepatic gluconeogenesis, blood sugar levels, cholesterol, triglycerides, and body weight. They also increase insulin secretion from beta cells (18). In a study on animals, the histological evaluation of the sciatic nerve showed that the diabetic animals treated with the oral use of *N. sativa* could reduce morphological alterations. Also, myelin breakdown was significantly reduced, and the ultra-structural properties of axons were significantly improved (19).

Despite these studies, there is no available evidence on the effect of topical *N. sativa* on diabetic peripheral neuropathy (DPN). Therefore, in the present research, it is hypothesized that topical *N. sativa* products may play a potential therapeutic role in decreasing the symptoms of DPN. In this regard, a topical Nigella Sativa product and gabapentin capsules are compared in terms of their effect on diabetic peripheral neuropathy.

2. Materials And Methods

This study was performed as a double-blind clinical trial on 120 patients with painful diabetic neuropathy. They gave their conscious consent to enter the study. Method of determining the sample size in this study is the use of parallel formula in three groups in which alpha is equal to 0.05 and beta is equal to 0.20. According to this formula, the number of participants in this study for each group of 40 people in total 120 views Was taken and the method of simple was used to randomize this statistical population; In this study, only the principal investigator and outcome assessor are aware of the contents of the envelope. Patients and others involved in the design have no information about the type of material in the envelopes. *N. sativa* and placebo are similar in shape, color, odor, packaging, and appearance, and blinding has been performed between them. Gabapentin capsule group is the standard treatment. Conscious consent was taken to enter the study. This was based on the ethics code IR.SSU.REC.1398.077 and the IRCT code IRCT20160221026684N2.

The participants were selected from residents of Yazd aged 30 to 70 years with HbA1c of less than 9. The exclusion criteria were spinal disorders, discopathy, uncontrolled blood sugar, sever cardiac, renal or
hepatic disorders, active foot ulcers, autoimmune diseases, mental illnesses, drug and alcohol addiction, skin lesions below the knees and feet and severe foot vascular diseases. The patients were examined by the Michigan Neuropathy Screening Instrument (MNSI). Those with an MNSI score of \( \geq 2.5 \) were diagnosed as DPN (20). Then, they were randomly divided into three groups. The first group received a topical N. sativa product (as a 10% ointment), the second group was given a topical placebo, and the last group received 300 mg gabapentin capsules. The patients were followed for eight weeks. The first follow-up was at the end of the second week to check for the complications and patient involvement. The second follow-up was at the end of the fourth week, and the third follow-up came after eight weeks. The MNSI questionnaire was the tool to assess the severity of neuropathic symptoms, and a higher score would mean more severity. The first part of the study was done with a questionnaire that consisted of 15 items on the patient’s self-report of symptoms, and each item had a score. The second part was a lower extremity examination that included a vibration perception test, a check on Achilles tendon tensile reflexes, and a monofilament test (21, 22). After the data collection, the studied variables were subjected to quality control and then statistically analyzed with the SPSS software version 20.

3. Remedy Preparation

Seeds of N. sativa were purchased from a local market in Yazd, Iran, and then approved by Dr. Mohammad Kamalinejad. After systematic authentication, a voucher specimen (SBMU-8029) was deposited at the Herbarium of the School of Pharmacy affiliated to Shahid Beheshti University of Medical Sciences. To prepare an aqueous extract, 100 grams of Nigella sativa seeds was added to one liter of distilled water and boiled for 20 minutes in a beaker. After cooling, the content of the beaker was filtered and then condensed using a rotary evaporator. Finally, 10 grams of the concentrated extract was obtained. In order to prepare N. sativa ointment (10%), 10 grams of the concentrated extract was added to 90 grams of Euchring 400% (SEPIDAJ PHARMACEUTICAL Co, Iran). A placebo ointment was also prepared with the same color, smell and packaging as the N. sativa ointment.

4. Results

This clinical trial was conducted for eight weeks, and three groups each including 40 people participated in it. The first follow-up was done in person, but the next one was done by phone due to the escalation of the corona pandemic. During this follow-up, a number of participants were unwilling to cooperate due to having coronary heart diseases; therefore, they stepped out of the project. In total, there remained 31 people in the N. sativa group. In the placebo group and the gabapentin group, 11 and 27 people took part in the analysis (Fig. 1). There were no side effects observed in any of the three groups.

These three groups were not significantly different in terms of age (P-value: 0.0695), MNSI score (P-value: 0.0167) and HbA1c (P-value: 0.865). (Table1)
Table 1
Age and score variables and HbA1c values reported as mean (± SD) a content (percentage)

<table>
<thead>
<tr>
<th>variable</th>
<th>N. sativa</th>
<th>Placebo</th>
<th>Gabapentin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.94 (± 9.487)</td>
<td>62.09 (± 8.596)</td>
<td>63.30 (± 11.874)</td>
<td>0.695</td>
</tr>
<tr>
<td>MNSI score</td>
<td>6.03226 (± 1.657988)</td>
<td>5.59091 (± 1.594023)</td>
<td>5.18519 (± 1.732873)</td>
<td>0.167</td>
</tr>
<tr>
<td>Hba1c</td>
<td>7.5412 (± 1.46717)</td>
<td>7.7714 (± 1.85447)</td>
<td>7.4059 (± 1.42059)</td>
<td>0.865</td>
</tr>
</tbody>
</table>

The results of the study were obtained based on the participants’ answers in the Michigan questionnaire before and after taking each of the drugs, i.e., gabapentin, placebo and N. sativa ointment, as well as the corresponding statistical comparisons. The main results are provided below.

There were reports of numbness and tingling sensation in the legs and feet in the groups taking the N. sativa (P-value: 0.00), placebo (P-value: 0.0341) and gabapentin (P-value: 0.003), prinking feeling in feet or legs in N. sativa ointment (P-value: 0.00), placebo (P-value: 0.15) and in Gabapentin group (P-value: 0.001). Also, the aggravation of symptoms at night was reduced in N. sativa (P-value: 0.00), placebo (P-value: 0.74) and gabapentin (P-value: 0.001) groups, but the reduction was significant in the N. sativa group with the gabapentin group next to it.

The patients in all the groups felt uncomfortable with bed sheets stretched on their feet, with P-values of 0.00, 0.153 and 0.001 for the N. sativa, placebo and gabapentin groups, respectively. Moreover, feeling uneasy when walking was reported by the groups that took the N. sativa (P-value: 0.0327), placebo (P-value: 1) and gabapentin (P-value: 0.613). In both cases, only the group consuming N. sativa experienced a significant decrease of the adverse feelings.

Muscle cramps in the groups taking the N. sativa (P-value: 0.00), placebo (P-value: 0.00) and gabapentin (P-value: 0.00) reduced significantly, so did burning sensation in the legs with P-values of 0.00, 0.00 and 0.00 for the N. sativa, placebo and gabapentin groups respectively. However, the reduction in muscle cramps after using N. sativa was significantly more than that in the other two groups.

However, in the study of the participants’ answers to the question about the recognition of cold and hot water when showering, there was no statistically significant difference among the N. sativa, placebo and gabapentin groups, with the P-values of 0.326, 1 and 0.83, respectively (Table 2).
Table 2
Analytical results for the answers to a number of Michigan questionnaire items before and after using N. sativa, placebo and gabapentin: The values are reported as means (± SD) and P-values.

<table>
<thead>
<tr>
<th>Question</th>
<th>N. sativa</th>
<th>P-value of N. sativa</th>
<th>placebo</th>
<th>P-value of Placebo</th>
<th>gabapentin</th>
<th>P-value of gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legs and feet numb</td>
<td>After</td>
<td>77.42 (± 42.502)</td>
<td>0.00</td>
<td>45.45 (± 52.223)</td>
<td>70.37 (± 46.532)</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>42.58 (± 33.113)</td>
<td></td>
<td>43.64 (± 50.452)</td>
<td>57.78 (± 42.161)</td>
<td></td>
</tr>
<tr>
<td>Burning pain in feet or legs</td>
<td>After</td>
<td>96.77 (± 17.961)</td>
<td>0.00</td>
<td>100.00 (± .00)</td>
<td>92.59 (± 26.688)</td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>49.84 (± 28.240)</td>
<td></td>
<td>75.00 (± 18.574)</td>
<td>65.37 (± 36.740)</td>
<td></td>
</tr>
<tr>
<td>Get muscle cramps in feet or legs</td>
<td>After</td>
<td>60.00 (± 50.00)</td>
<td>0.00</td>
<td>100.00 (± .00)</td>
<td>66.67 (± 48.154)</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>9.00 (± 20.666)</td>
<td></td>
<td>36.00 (± 36.803)</td>
<td>13.54 (± 24.069)</td>
<td></td>
</tr>
<tr>
<td>Prickling feeling in feet or legs</td>
<td>After</td>
<td>87.10 (± 34.078)</td>
<td>.00</td>
<td>81.82 (± 40.452)</td>
<td>81.48 (± 39.585)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>40.65 (± 32.320)</td>
<td></td>
<td>67.73 (± 44.574)</td>
<td>56.30 (± 41.501)</td>
<td></td>
</tr>
<tr>
<td>It hurts when the bed covers touch the skin.</td>
<td>After</td>
<td>40.00 (± 49.827)</td>
<td>.005</td>
<td>44.44 (± 52.705)</td>
<td>38.46 (± 49.614)</td>
<td>.0078</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>19.67 (± 35.693)</td>
<td></td>
<td>38.33 (± 47.828)</td>
<td>30.38 (± 43.930)</td>
<td></td>
</tr>
<tr>
<td>Able to tell the hot water from the cold water</td>
<td>After</td>
<td>3.45 (± 18.570)</td>
<td>.326</td>
<td>0.00 (± .00)</td>
<td>11.11 (± 32.026)</td>
<td>.83</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>0.69 (± 3.714)</td>
<td></td>
<td>0.00 (± 0.00)</td>
<td>1.11 (± 3.20300)</td>
<td></td>
</tr>
<tr>
<td>Symptoms worse at night</td>
<td>After</td>
<td>80.00 (± 40.684)</td>
<td>.000</td>
<td>63.64 (± 50.452)</td>
<td>70.37 (± 46.532)</td>
<td>.001</td>
</tr>
</tbody>
</table>
5. Discussion

Diabetic neuropathy is one of the most common micro-vascular complications of diabetes (23). It is important to adopt certain strategies to suppress the symptoms of this disease, prevent its progression and treat it (24).

Neuropathy usually requires long-term treatment. In this regard, due to the side effects of oral therapies, topical therapies are more tolerable especially to the elderly as well as diabetic patients with renal and hepatic complications (6, 25).

According to the results of this study, some symptoms of diabetic neuropathy, such as discomfort in pulling a bed sheet over the feet and sensation in the feet when walking, were significantly reduced in those who received N. sativa as compared to the other groups. Regarding numbness and tingling sensation in the legs and foot soles as well as the worsening of symptoms at night, both N. sativa and gabapentin groups experienced a significant decrease, but the former was at a better stance than the latter. These results may indicate the effectiveness of N. sativa in improving the symptoms of diabetic neuropathy. So far, no clinical study has been conducted to evaluate the effects of N. sativa topically in the treatment of diabetic sensory neuropathy, but the neuroprotective effects of N. sativa have been shown in some studies. As Seghatoleslam et al. (26) showed, Nigella sativa is able to prevent hippocampal neural damage. Also, Feyzi Çelik et al. (27) showed that thymoquinone is beneficial for decreasing the experimental neuropathic pain following an experimentally applied spinal cord injury. In another study, Islam et al. (28) noted the neuroprotective effects of N. sativa extracts during germination on the central nervous system were noted. Moreover, the analgesic and anti-inflammatory activity of N. sativa were examined in previous studies (15, 29, 30). According to some studies, N. sativa and its active constituent, thymoquinone, have angiogenic and ischemic effects (31). This is important due to the role
of endometrial micro-vascular abnormalities and ischemia driven by hyperglycemia and the metabolic change in the pathogenesis of diabetic neuropathy (32). Despite these attempts, the exact mechanism of N. sativa to alleviate diabetic neuropathy remains unclear and needs further investigation.

In this research, the examination of a number of symptoms such as burning sensation in the foot soles and muscle cramps showed a significant decrease of those symptoms in all the three groups. In several studies, the response to placebo increased in drug trials (33). So, one of the areas of interest in recent decades has been the study of how placebo affects the response to treatment and what psychological, neurological, biological and genetic mechanisms are involved in the treatment of the disease (34, 35).

The main limitation of this study was its concurrence with the Covid-19 pandemic. In order to reduce the risk of coronavirus infection in the volunteers, all the follow-ups, except for the first visit, were done by phone. One other hand one of the strengths of this study is the topical application of this substance, and due to the fact that the target group often has restrictions on the use of the N. sativa, this drug is due to the way it is used, except in rare cases that show mild skin allergies. There are no other reports on the side effects and limitations of its use.

6. Conclusion

In general, a topical N. sativa cream significantly improves the symptoms of diabetic neuropathy. It is even more effective than synthetic Drug Gabapentin. Since topical administration of this N. sativa does not cause any specific side effect, it can be considered as one of the options to treat patients with this disease. This mostly holds in the upper age group. As a recommendation for future research, other complications of diabetes such as kidney and liver disorders may be explored.

References


Figure 1

Summary of study flow diagram