THE EFFECT OF NIGELLA SATIVA L. ON INTRACTABLE PEDIATRIC SEIZURES

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Abstract:
Background:
Despite availability and administration of numerous antiepileptic drugs (AEDs) nearly 15% of childhood epilepsy cases are resistant to treatment; in traditional medicine however Nigella sativa L. (Black seed) has been known for its anticonvulsant effects.
Materials and Methods:
In this double–blind clinical trial conducted on children with refractory epilepsy we administered the aqueous extract of black seed as an adjunct therapy and compared the effects with those of a placebo. The study was performed between Sep 2003 and Nov 2004. The subjects received either extract or placebo for a period of four weeks and between these two periods for two weeks they received only their pre-existing anti-epileptic drugs (AEDs).
Results:
The mean frequency of seizures decreased significantly during treatment with extract, (p-value = 0/007).
Conclusion:
It can be concluded that the water extract of Nigella sativa L. has antiepileptic effects in children with refractory seizures that do not respond to known AEDS.
keywords: Nigella sativa, Intractable seizures, Children

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Introduction

Despite administration of numerous antiepileptic drugs (AEDs) nearly 15% of childhood epilepsy cases are resistant to treatment; these drugs fail to provide adequate control of epileptic seizures and do not prevent progressive epileptogenic changes (1,2). Recurrent seizures are still common clinical problems of hospitalized pediatric patients (3).

Black cumin seed (botanical name is Nigella sativa L, Ranulacea family) or “Black seed” for short; although believed to be indigenous the Mediterranean region, has been cultivated in other parts of the world; through the years it has played an important role in ancient Islamic medical practice. Much research is available on its various therapeutic effects such as anti cancer (4), diuretic and hypotensive effects (5), antihistaminic (6,7), antihypertensive (8), hypoglycemic (9) anti-inflammatory, analgesic (10), antifungal and antibacterial (11,12). The oil is useful in diseases

in which free radicals are involved, e.g. anoxia and ischemia of brain and heart as well as arteriosclerosis, rheumatism and cancer (8,11,13,14,15).

In ancient Islamic medicine, Nigella sativa (Black cumin) was known for its anticonvulsant effects. (16) Black seed, in particular its major constituent thmoquinine, have recently shown antiepileptic effects in mice. (17,18). Furthermore several studies based on the toxicity of black seed have been reported. It has been shown that there were no toxic effects when Nigella sativa seed oil was given to the mouse via the stomach; it has been also reported that the nigella seed powder does not produce any toxic effect when given to rabbit again by gastric intubation (19). Also acute and chronic toxicity of Nigella sativa fixed oil was investigated in rats and mice and there were no evidence of toxicity (20) In this study we have assessed oral administration of black seed aqueous (soxhlet) extract as an adjunct to AEDs in a double-blind clinical trial and compared the results with those of a placebo.

Materials &Methods:

This pilot study was performed between Sep 2003 and Nov 2004, in a tertiary referral center (Ghaem medical center, Mashhad, Iran) Black cumin seeds were collected from the southern part of the Khorasan province in Iran. Patients and their relatives were advised that black seed extract was registered for sale in USA as an immune modulator (21), but without proven efficacy in epilepsy and asked to give informed consent.

To be included in this pilot study, patients had to have intractable epilepsy according to definition. (22), occurrence of at least one seizure during the four-week baseline period, relative absence of confounding illnesses, constant antiepileptic treatment at least one month before the study.

Exclusion criteria were history of status epilepticus within the three months prior to the first visit, history of pseudo seizures, seizures that due to their fast and repetitive nature could not reliably be counted, current renal and cardiac or hepatic dysfunction and lack of co-operation. Patients who, qualified for the inclusion criteria, were selected in sequential order of presentation from the routine clinical caseload. Based on their type of seizures and poor control with established AEDs, they were selected over a consecutive period of 11 months; in this period of time 23 patients were enrolled, but only 20 completed the study. The number of patients was deemed to be a sufficient sample size of a pilot study. Initially, prior to enrollment, each child underwent clinical examinations, both general and systemic. Patients were visited once a week throughout the study and all information related to the number of seizures, history of duration of, or possible changes in, seizures was obtained from the parents. The clinicians were made familiar with the nature and treatment history of patient's epilepsy. Diagnosis of intractable seizures was made prior to the study and type of seizures were categorized according to ILAE classification (23,24).

Patients were provided with the syrup free of charge; they received either extract or placebo at the dose of 0/4 ml/kg/8h for four-weeks and after a period of wash –out (2 weeks) they received the other (extract or placebo for the same period). The dosage of concomitant AEDs was maintained throughout the treatment period. Throughout these periods, the number, type and duration of seizures were registered; in addition any adverse effects that occurred were reported to the clinician and his assistant. This protocol provided a uniform measure of seizure frequency for comparison and contrast. At the end of each period (placebo or extract) the degree of parental satisfaction was assessed.

The study was reviewed and approved by the Research and Ethics Committee of Mashhad University of Medical Sciences of Iran.

All analysis was made using the SPSS statistical software package and probability value of less than 0.05 was considered statistically significant.

Results:

20 patients were eventually enrolled for the pilot study (10 girls and 10 boys), ranging in age from 13months to 13 years (mean 66.95 ± 45.39 months).

Seizure types were: 4 patients- generalized tonic-clonic, 8 myoclonic, 2 complex partial seizures, 1 polymorphic seizure, 3 absence, 1 myoclonic with generalized tonic-clonic,1 tonic-clonic with infantile spasm attack. 25% were mentally retarded or had abnormal findings in their neurological examinations.

Electroencephalograms (EEGs) and Computed tomogram (CT-Scans) were abnormal in 90% and 20% respectively. Mean age of seizure onset was 19.15 ± 23.06 months.

Patients used between 2 and 5 AEDs at time of entry in to the study. Compliance with extract was found to be very good, as verified by remaining syrup at the end of each week.

The mean frequency of seizures in children at the end of extract period decreased from 5.78 ± 7.2 seizures / day before initiation of the study, to 4.21±5.77 seizures/day. At the end of the placebo period, mean frequency of seizures reached to 6.14±6.75 seizures / day. The results of Friedman statistical test on these data showed a significant difference in seizure frequency between extract period and other periods (Pvalue <0/001). Since the number of seizures in children varied widely, there was a need for testing of data using a non- parametric statistical test, independent of the mean, and hence the "Wilcoxon test" was used, the results demonstrating a significant difference between the extract period and the period before initiation of the study, with p value of 0.007. Data from these two periods were compared weekly with the Wilcoxon test; it seems that a statisticallysignificant difference between extract and placebo period. (Table 1)

Table-1: Results of the Wilcoxon test for frequency of seizures/day

Seizures / Time	First week	2nd week	3rd week	4th week
Extract period	6±7.44	5.03±7.31	4.74±6.89	4.21±5.77
Placebo period	5.55±7	5.34±6.79	5.7±7.14	6.14±6.75
P value	0/381	0/132	0/011	0/001

The degree of parental satisfaction at the end of extract period and placebo period also showed a significant difference. (Table-2).

Table-2: Parental satisfaction at the end of each period

Time/Satisfaction	Satisfied	Ineffective	Dissatisfied
Extract period	75%	25%	0%
Placebo period	30%	50%	20%

During this study 3 patients reported adverse effects. One patient was constipated in the 2nd and 3rd weeks of the extract period; in another, the parents reported increased laughing at the time of seizure, during the placebo period; in the third, maculopapular rash appeared on the trunk on day 28.

Discussion

Recurrent seizures and intractable epilepsies are common clinical problems of hospitalized pediatric patients, constituting a considerable number of outpatients referring to pediatric neurology clinics. In spite of advances in the treatment of epilepsy, a significant number of children with epilepsy do not respond appropriately to antiepileptic drugs (AEDs) (1,3).

Although an intensive search of literature failed to reveal any clinical trial on the anticonvulsant effects of Nigella sativa L on humans, the same effect in thymoquinine, the major constituent of Nigella sativa l. have been investigated in mice using pentylenetetrazole (PTZ)- and maximal electroshock (MES)- induced seizure models. In this study thymoquinone did exhibit anticonvulsant activity in the PTZ – induced seizure model, but no similar activity was seen in the MES model (17). Generally, compounds with the anticonvulsant activity in petit mal epilepsy, are effective in PTZ – induced seizure models and drugs that possess anticonvulsant activity in MES, may be considered as an effective against grand mal epilepsy (25). It can hence be concluded that thymoquinone may be useful in petit mal epilepsy, through an opioid–mediated increase in the GABAergic tone mechanism (17).Recently anticonvulsant and antioxidant effects of Nigella sativa oil against PTZ-induced kindling in mice were investigated, this study clearly demonstrated a potent anticonvulsant property for Nigella sativa oil against the development of kindling consequences in PTZ-kindled mice, and was more potent as an anticonvulsant agent than Valporate when they were compared experimentally. The mechanism for the anticonvulsant effect seems to be correlated with the antioxidative effect. (18).

In our study, during the extract period, the mean of seizures decreased gradually, whereas this was not so in the placebo period.

At the end of the fourth week of the Nigella sativa period, 3 children had become seizure free; two of them had myoclonic seizures. In one patient with Lennox-Gastaut the number of seizures in the extract period was more than in the placebo period. Results of our study showed that aqueous extract of Nigella sativa has and anticonvulsant effect, which may be explained by thymoquinone the major constituent of Nigella sativa seeds. Furthermore oil and fatty acids of Nigella sativa seeds seem to play a role in this effect.

Conclusion

On the basis of the above observations, it may be concluded that the aqueous extract of Nigella sativa L. has anticonvulsant effects and can improve seizure control in children suffering from refractory epilepsy. There is however the need for more extensive trials to be conducted in such patients to confirm these preliminary findings.

Acknowledgment:

We wish to express our appreciation to he vice-chancellor for research of Mashhad University of Medical Sciences for supporting this study. We especially wish to thank Dr.Habib Esmaili for the statistical review of this study.

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