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Local Usage of *Nigella sativa* Oil as an Innovative Method to Attenuate Primary Dysmenorrhea: A Randomized Double-blind Clinical Trial

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ABSTRACT

Objectives: We sought to determine the effect of topical application of *Nigella sativa* (black seed) oil, on the primary dysmenorrhea intensity. ***Methods***: We conducted a randomized, double-blind clinical trial on 124 female students, 18–22 years old, living in the dormitories of Sabzevar Universities. After a primary assessment, participants were randomly divided into two groups. The first group rubbed two drops of *N. sativa* oil, and the second group rubbed liquid olive oil, as the placebo. Massage was performed on the fontanel lobe 3, at night, three days before menstruation, for eight consecutive days (about five days after menses). This procedure was repeated for three menstrual cycles. After three cycles, pain severity was measured by the visual analog scale. Data analysis was carried out using the Mann-Whitney U test and analysis of covariance (ANCOVA). ***Results:*** This study was conducted on 124 female students. The mean age of students, mean age of first menarche, body mass index, and pain severity were not significantly different in the two groups ($p > 0.050$). No adverse effects were observed during the study. The results of ANCOVA showed that pain intensity in *N. sativa* oil group was significantly decreased compared to that of the placebo group (0.6 score; $p < 0.050$). ***Conclusions:*** *N. sativa* could be a promising, safe, and easily available analgesic supplement in women suffering from primary dysmenorrhea.

Dysmenorrhea or period pain refers to the symptoms of painful cramps in uterine, originating around the time of menstruation. It can be divided into primary and secondary pain. Primary pain occurs in the absence of pelvic pathology, and the secondary form results from an identifiable organic disease.[1] Dysmenorrhea is the most common reason for school or workplace absence. It can be crippling, both physically and psychologically, and has some consequences on the individual, social, and economic dimensions. The prevalence of dysmenorrhea is estimated to be up to 90% in adolescents, and up to 15% of these women have a level of pain that interferes with their quality of life.[2]

Pain usually begins one or two days before menses and typically lasts 24–72 hours. It is felt in the lower abdomen, back, or thighs and can be accompanied by nausea, vomiting, fatigue, and even diarrhea.[3] Pain from secondary dysmenorrhea usually begins earlier in the menstrual cycle and lasts longer than primary menstrual cramps. This pain is typically accompanied by nausea, vomiting, fatigue, or diarrhea. Some of the risk factors for primary dysmenorrhea include early onset of menstrual periods (before the age of 12), heavy or prolonged menstrual flow, a prior family history of dysmenorrhea, obesity, a history of smoking, or high levels of stress.[4] Contractions take place due to the release of prostaglandins and a decrease in blood circulation. Lipid peroxidation and decrease in antioxidant levels are thought to play an important role in this situation, indicating the occurrence of oxidative stress.[5]

There are two main approaches for attenuating primary dysmenorrhea: drug and non-drug treatments, or complementary medicine. Drugs such as acetaminophen, and especially non-steroidal anti-inflammatory drugs (NSAIDs), including diclofenac,

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ibuprofen, and naproxen, can effectively relieve the pain of primary dysmenorrhea.[6] NSAIDs inhibit prostaglandin production. However, these drugs are associated with several side effects, including drowsiness, gastrointestinal problems, renal, and cardiovascular adverse effects.[7,8] On the other hand, some women do not like to use drugs and prefer to suffer from existing pain. In addition to conventional medicine, complementary herbal remedies, nutrition, acupuncture, aromatherapy, massage therapy, chiropractic, reflexology, homeopathy, and yoga are some methods that attenuate pain in patients. There are several herbal remedies such as saffron, ginger, black cumin, thyme, celery seed, and omega-3 that have been used in traditional medicine to treat primary dysmenorrhea.[9–11]

Nigella sativa (Ranunculaceae family), also known as black seeds, is a widely used plant in traditional medicine. This plant has been prescribed for treating many disorders and diseases such as cough, asthma, nasal congestion, headache, dental pain, gastrointestinal diseases, menstrual disorders, and impotence.[12] The literature regarding the pharmacological activities of this herb and bioactive components are extensive: cardioprotective,[12,13] anti-hyperlipidemic,[14] anticancer,[15] hepatoprotective,[16] nephroprotective,[17] anti-inflammatory,[18,19] anti-seizure,[20] and antioxidant effects are some of the biological properties of this ancient plant.[21,22] In a randomized, triple-blind clinical trial, *N. sativa* fixed oil has been useful for mastalgia, comparable to diclofenac.[23] However, its effects on dysmenorrhea in humans is of interest.

In this study, we decided to evaluate the topical administration of black seed oil in young women suffering from dysmenorrhea. The oil was applied as one to two drops on the fontanel area, for one to two minutes with a gentle massage.

METHODS

We conducted a randomized, double-blind placebo-control clinical trial on female students aged 18–22 years old living in the dormitories of Sabzevar Universities of Medical Sciences, as well as Hakim Sabzevari University. Data were gathered from October 2013 to March 2014. The Ethics Committee of Sabzevar University of Medical Sciences approved the research proposal, and all participants signed a consent form. This work was registered in the Iranian Registry of Clinical Trials (Number 2014033117109 N1).

The inclusion criteria for participants were: aged 18–25 years old, having a regular menstrual cycle, not being affected by depression or anxiety, not having an acute or chronic disease, not taking medicines or supplements, and not taking regular exercise.

The exclusion criteria were: pregnancy, taking NSAIDs, willingness to use hormonal contraceptive drugs or taking any hormonal treatment, or not filling out the forms regularly. Patients were also excluded from the study if they were unwilling to continue the treatment and had a history of medical problems or genitourinary system surgery.

After a primary assessment with the demographic questionnaire by a gynecologist, students that met the inclusion criteria were asked to participate in the study. We used the standard methods to measure height and weight. The participants were then randomly divided into two groups. Participants in both groups were matched in terms of the duration of dysmenorrhea and pain severity. The samplers and participants were kept blinded to treatment allocation.

The first group rubbed one to two drops of *N. sativa* oil on fontanel lobe 3 of the head, at night, three days before their menstruation period, and up to five days after. This regimen was repeated for three menstrual cycles. The second group rubbed a placebo oil (olive oil) in the same way. The *N. sativa* and olive oil were purchased from Barij Essence Company (Kashan, Iran). Both products were prepared in similar packages by the company so that neither researcher nor patients could distinguish the difference.

Before and after three menstrual cycles, participants filled the pain intensity form. Pain severity was measured by the visual analog scale (VAS) in both groups at the beginning and end of the study.[24] The VAS is designed for six grades of severity (none, very mild, mild, moderate, severe, and very severe).

Subjects were advised not to change their dietary habits, physical activities, and drug regimens during the study.

We determined the degree of compliance for each participant according to the volume of oil left in the jar. The compliance of all subjects was more than 90%, and participants reported no adverse effects.

Table 1: Demographic characteristics of patients in the *Nigella sativa* oil and placebo groups.

Variables	Total	*N. sativa* (n = 69)	Placebo (n = 55)	*p*-value
Age, years	20.5 ± 0.2	20.8 ± 0.2	20.2 ± 0.3	0.100
Age of menarche, years	13.5 ± 0.1	13.6 ± 0.1	13.3 ± 0.2	0.330
Age of experiencing dysmenorrheal, years	15.3 ± 0.3	15.5 ± 0.3	15.2 ± 0.3	0.620
BMI, kg/m^2	21.2 ± 0.4	21.4 ± 1.5	21.4 ± 1.7	0.460

BMI: body mass index. Data presented as mean±standard deviation.

Table 2: The comparison pain score in the *Nigella sativa* oil and placebo groups before and after the intervention.

Variables	Before	After	*p*-value
N. savita oil	5.1 ± 0.3	3.4 ± 0.3	< 0.001
Placebo	5.8 ± 0.2	4.3 ± 0.2	< 0.001
p-value	0.14	0.006	-

Data presented as mean±standard deviation.

Data analysis was carried out using R software, version 3.2.1. The mean dysmenorrhea severity scores was measured before, and three cycles after the intervention. The difference between the two groups was analyzed using the Mann-Whitney U test. Data were compared in pairs via the analysis of covariance (ANCOVA), and modification of the level $p < 0.050$ was considered significant.

RESULTS

This study was performed on 124 female students. The demographic characteristics, including mean age of students, mean age of first menarche, age of experiencing dysmenorrhea, and body mass index showed no significant difference between groups ($p > 0.050$, Table 1).

The pain decreased in both groups ($p < 0.001$, Table 2) by the end of the study. However, this reduction was more in the *N. sativa* oil group. There was no significant difference between the two groups before the intervention ($p = 0.140$), it was significant after ($p = 0.006$, Table 2).

We used ANCOVA to calculate the pain score reduction. The analysis showed a significant reduction of pain score equal to -0.6±0.3 ($p = 0.046$, Table 3) in the *N. sativa* oil group in comparison to the placebo group.

DISCUSSION

In our study, the mean age of menarche was 13.5±0.1, which was similar to the previous studies.[25] Although menstrual pain starts from the first day of menstrual flow, we measured the prophylactic effect of *N. sativa* oil by applying it three days before the start of menstruation and continuing for eight consecutive days (about five days after the end of menses).

The aim of adding a placebo group was to exclude the positive effect that massage might have on the pain scores. By decreasing the levels of the stress hormone, massage increases the endorphins levels in the plasma and following that the neurotransmitter, serotonin. This neurotransmitter is involved in modulating the ascending and descending pain pathways. As a result, the conduction of pain is inhibited.[26]

Table 3: Analysis of pain score before and after the intervention according to analysis of covariance coefficients.

Model	Unstandardized Coefficients B	Standardized Coefficients B	*p*-value
Constant	1.9 ± 6.4		0.003
Pain score before treatment	0.5 ± 0.0	0.577	< 0.001
Pain score after treatment with *N. sativa* oil	-0.6 ± 0.3	-0.148	0.046

N. savita: Nigella savita. Data presented as mean±standard deviation.

Our results showed that *N. sativa* possesses an analgesic activity by decreasing the intensity of pain among those who suffered from dysmenorrhea.

Complementary and alternative medicine has shown acceptable results in comparison to conventional treatments in different ailments. In a randomized, double-blind clinical trial, aromatic oil massage consisting of *Lavandula officinalis*, *Salvia sclarea,* and *Origanum majorana* relieved pain and reduced the duration of menstrual pain.[25]

About 36–38% of black cumin seed is fixed oil. This lipid fraction consists mainly of thymoquinone (30–48%), thymohydroquinone, dihydro-thymoquinone, tocopherols including α-, β-, γ- and δ-tocopherol, thymol, cymene, trans-anethole, 4-terpineol, as well as carotenoids, which may contribute in the pharmacological actions of fixed oil.[27]

Prostaglandins are potent proinflammatory mediators produced by cyclooxygenase enzymes 1 and 2 (COX-1 and COX-2) in the myometrium of the uterine wall. The contributory role of prostaglandins, especially prostaglandins E2 (PGE2) and F2 alpha (PGF2α), has been demonstrated in the pathogenesis of dysmenorrhea.[28,29] Myometrial contraction due to the elevated levels of such mediators is responsible for the observed pain. Headache, nausea and vomiting, backache, and diarrhea are also other consequences of prostaglandins release. Thymoquinone showed an anti-inflammatory effect in a mouse model of allergic airway inflammation.[30]

In an in vitro study, dithymoquinone, thymohydroquinone, thymol, and thymoquinone showed significant inhibitory activity against COX enzymes comparable to indomethacin. Thymol inhibited more COX-1 with an inhibitory concentration (IC50) of 0.2 μM, while thymohydroquinone and thymoquinone were most active against COX-2, with an IC50 of 0.1 and 0.3 μM, respectively.[31] A cancer chemopreventive effect of *N. sativa* volatile oil was reported in a rat multi-organ carcinogenesis bioassay by lowering PGE2.[32]

Moreover, pain is associated with increased levels of lipid peroxidation and decreased superoxide scavenging activity.[33] It is well documented that the elevated levels of free radicals and/or lowered antioxidant potential lead to oxidative stress. Oxidative stress induced in this situation contributes to pain and other symptoms associated with dysmenorrhea.[34]

The average daily intake of antioxidants, beta carotene, vitamin-E, and zinc was significantly higher in girls without dysmenorrhea compare to their dysmenorrheic counterparts.[35] In a rat model of neuropathic pain, thymoquinone attenuated pain manifestations by lowering the spinal malondialdehyde, a marker for oxidative stress, and increasing the glutathione as an antioxidant factor.[18] However, one study found no relationship between the levels of oxidative markers and the severity of dysmenorrhea.[36]

Many women with dysmenorrhea suffer from increased uterine contractions.[37] The volatile oil of *N. sativa* seeds attenuated spontaneous movements of uterine, as well as oxytocin-induced contractions, in an in vitro study using isolated uteruses of rats and guinea pigs. They suggested that this volatile oil may have some anti-oxytocic potential.[38]

One of the advantages of this study is that the fontanel application of oil is a simple and convenient route of drug administration for patients. Delivery of drugs in this way avoids the hepatic first-pass metabolism and, as a result, improves the bioavailability of the drug.[39] In a recent study, topical administration of *N. sativa* oil was safely used for the treatment of imiquimod-induced psoriasis-like lesions in rats.[40]

The limitation of our study was the lack of a control group without any intervention and a massage alone group. Additionally, the method of massage in the fontanel lobe was not compared with other pressure points for the relief of pain. Therefore, we recommend that other studies will be required with more control groups to compare the effectiveness of the procedure.

Anxiety, depression, and premenstrual syndrome (PMS) are common complications linked with dysmenorrhea.[41,42] Conventional antinociceptive drugs used in this period, such as NSAIDs, do not affect these complications. In an in vitro study, *N. sativa* methanolic extract increased inhibitory neurotransmitter gamma amino butyric acid, and decreased excitatory neurotransmitter glutamate in the cultured neurons.[43] The sedative effects of *N. sativa* has been reported in previous studies, which could be a beneficial effect in dysmenorrhea.[44]

CONCLUSION

Our study suggests that the application of *N. sativa* oil on the fontanel lobe at night could have an analgesic effect that helps to relieve menstrual pain.

Considering that the use of massage is an inexpensive method with little or no side effects, patient compliance is high. Contribution of different active moieties could be responsible for the beneficial effects observed with the *N. sativa* oil, which may act synergistically.

Disclosure
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