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EFFECT OF NIGELLA SATIVA NASAL OIL DROPS ON SYMPTOMS SEVERITY AND TREATMENT SATISFACTION AMONG PATIENTS WITH CHRONIC RHINOSINUSITIS: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Chronic rhinosinusitis is a prevalent and complex disease associated with symptoms that interfere with patients' quality of life. Although there are many treatment options, they are linked with side-effects and high patients' dissatisfaction. Little studies were conducted to test the effect of Nigella sativa (N. sativa) on chronic rhinosinusitis which is known for its beneficial effects on inflammation. Therefore, the aim of this trial is to examine the effect of N. sativa nasal oil drops on symptoms severity and treatment satisfaction among patients with chronic rhinosinusitis. Methods: This trial was performed as a prospective, open-labelled and comparative clinical trial design on 102 patients with chronic rhinosinusitis. Patients were randomly assigned to either the control group which used the standard medical treatment only or the study group that received N. sativa nasal oil drops in addition to the standard medical treatment for four consecutive weeks. Outcomes were assessed five times; once every two weeks for eight consecutive weeks using Sino-nasal Outcomes Test-22 and Treatment Satisfaction Questionnaire for Medications, where the total scores were compared between both groups using two independent samples t-test. Results: Initial assessment showed no significant differences between both groups in the mean total scores of severity of symptoms and patient satisfaction. But, during and post-intervention assessments revealed significant differences between the two groups ($p \leq .005$) except satisfaction with side-effects. These differences sustained at the follow-up period as measured at the first and the second follow-up post-intervention assessments. The main trial's primary outcomes were nasal obstruction/congestion, postnasal discharge and facial pain/pressure, where the relative risks (RR) were 0.70, 0.48 and 0.42 respectively, whereas, the secondary outcomes were fatigue, reduced productivity, reduced concentration, frustration/restlessness/irritability, sadness and patient dissatisfaction. Conclusion: Nigella sativa nasal oil drops had a significant positive effect on severity of symptoms of chronic rhinosinusitis and patients' satisfaction, hence, it is recommended to be integrated with the standard medical treatment for those patients. Also further trials are recommended to support the positive effect of Nigella sativa on chronic rhinosinusitis. **Trial Registration no**: NCT05494164 (Registration date 9/8/2022 https://clinicaltrials.gov/study/NCT05494164).

Keywords: Nigella Sativa, Black Cumin, Chronic Sinusitis, Symptoms, Satisfaction.

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1. INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent and complex disease among adults as well as children and linked with a high disease burden on individuals and society as a whole [1], [2], [3]. It is defined as symptomatic inflammation of the paranasal sinuses and nasal cavity that lasts more than 12 weeks [4], [5]. Although the true prevalence of CRS cannot be estimated because of its overlap with other diseases and the presence of several diagnostic criteria, the prevalence has been estimated between 3% to 12% [6].

Chronic rhinosinusitis is associated with significant signs and symptoms that interfere with quality of life (QoL) including purulent nasal drainage; nasal obstruction or congestion; facial, ear and dental pain; headache; edema in the periorbital area; sore throat; snoring; hyposomia or ansomnia; unpleasant taste; anorexia; halitosis, chronic unproductive cough; chronic hoarseness; malaise and fatigue; visual disturbances and unexplained fever in some cases [5], [7], [8]. Moreover, CRS is associated with an increased likelihood of developing depressive symptoms and sleep problems [9], [10], [11]. Accordingly, CRS is commonly described as annoying and frustrating by many patients. Furthermore, several studies concluded that patients with CRS have poor QoL which negatively affects patient's functional, social, physical and psychological functions [10], [12], [13].

Chronic rhinosinusitis is mainly treated with symptomatic measures, yet, some cases may require surgical interventions [14]. However, many studies claimed that although different treatment options for CRS are associated with promising results, they are linked with high rates of recurrence as well as serious side-effects and all these led to the search for treatments that may improve outcomes and limit the treatment burden [15], [16].

Furthermore, Klonaris et al., [17] alleged that patients with CRS are frustrated and dissatisfied from lack of improvement with the current medical managements. Also, Okano et al., [16] reported low levels of treatment satisfaction among patients with CRS which is negatively correlated with the severity of symptoms. All these findings maximized the need for other treatments for CRS that may ameliorate patients' satisfaction. Nonetheless, herbal remedies are widely used as a complementary or even as an alternative therapy by those patients as a self-managing method to overcome annoying symptoms and patients' dissatisfaction with the current treatment; one of these herbal remedies is Nigella sativa (N. sativa) [17].

Recently, few studies indicated that the use of N. sativa in different forms may enhance the QoL of patients with CRS as signified by improved severity of symptoms [18], [19], [20], [21], [22]. These effects were explained by the fact that N. sativa oil inhibits the inflammation of sinuses and respiratory airways, microbial infections and help the patients with clinical symptoms of sinusitis [19]. Accordingly, it is highly recommended that clinical trials are required to evaluate the efficacy of N. sativa among patients with CRS in the near future. The nurse plays a key role in enhancing self-care for patients with CRS and building the best effective evidence to achieve high quality nursing care which consequently improves patient satisfaction and increases the autonomous role of the nurses [23]. However, there are limited data on specific nursing intervention regarding the

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use of N. sativa for chronic rhinosinusitis and its effect on the severity of symptoms and patient satisfaction. Therefore, the aim of the current clinical trial is to examine the effect of Nigella sativa nasal oil drops on symptoms severity and treatment satisfaction among patients with chronic rhinosinusitis.

Needless to say, little research studies were conducted to evaluate the actual effectiveness of these herbal remedies in assisting this group of patients. Accordingly, this trial was conducted upon the science of complementary and alternative medicine (CAM) that may be useful for nursing and other health care professionals in several ways. Professionals then may wish to incorporate N. sativa into already established intervention programs, and to find ways to stimulate and facilitate its usage as an adjuvant to professional services.

2. METHODS

2.1 Aim

The aim of the current clinical trial was to examine the effect of Nigella sativa nasal oil drops on symptoms severity and treatment satisfaction among patients with chronic rhinosinusitis. Primary outcomes represented common signs and symptoms of chronic rhinosinusitis, whereas, secondary outcomes exemplified some of the complications that may happen. To achieve the aim of the current trial the following research hypotheses were postulated:

H_1: The total severity of symptoms mean scores of patients with CRS who will use Nigella sativa nasal oil drops will be different from the total severity of symptoms mean scores of a control group.

H_2: The total treatment satisfaction mean scores of patients with CRS who will use Nigella sativa nasal oil drops will be different from the total treatment satisfaction mean scores of a control group.

2.2 Design

A prospective, open-labelled and comparative parallel form clinical trial design was utilized in the current study in which the study group who received N. sativa nasal oil drops was compared with a control group who received the standard treatment with a ratio of one to one and both groups were aware of the assigned treatment.

2.3 Setting

The current trial was conducted in the Ear, Nose and Throat (ENT) outpatient clinic at Kasr Al Ainy University Hospital, Cairo, Egypt.

2.4 Participants

Based on G power, the total sample size was calculated to be 102 adult patients, having a confirmed diagnosis of CRS by signs and symptoms and radiographic imaging showing sinus inflammation. The sample size was calculated adopting the effect size from the previous studies 0.65 and considering statistical power and significance level as 90 %

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and 5 % (two-sided) respectively. Participants were randomly assigned to either the study group (51) or the control group (51) using sealed envelopes to ensure allocation concealment. Pregnant or lactating women; patients receiving immunosuppressant, anticoagulant/antiplatelet or potassium sparing diuretic medications and patients with coagulation disorders, allergic to N. sativa, scheduled for surgical intervention or using any type of natural products as a complementary therapy at the time of the trial were excluded.

However, 14 participants withdrew from the trial, eight from the study group and six from the control group. The reason for attrition in the control group was that they either could not be contacted or scheduled for surgery, while in the study group, attrition was mainly due to discontinuing the treatment as they could not the burning sensation and headache that lasts for minutes after instillation of the drops at the initial doses.

2.5 Data Collection Tools

The first tool is Demographic and Medical Data Form (DMDF) which was developed by the researcher. The second tool is the Arabic version of Sino-Nasal Outcome Test 22 (SNOT-22) which was used to investigate the severity of symptoms; it consists of 22 items scored on five points Likert scale ranging from zero to five and the overall scores are ranged from 0 to 110 with higher scores suggesting symptom severity [24].

The third tool is the Arabic version of Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4. Which includes 14 items that assess four key dimensions of treatment satisfaction. It includes effectiveness, side-effects, convenience and global satisfaction. Scores for each domain are calculated and transformed into a value ranging from 0 to 100 [25], then total scores for each domain are transformed into two main categories as follow; “Dissatisfied” when the score is < 75 and “Satisfied” when the score is ≥ 75.

2.6 Procedure

The seeds of N. sativa and sesame were bought from a well-known market for selling/buying medicinal herbs in Egypt, then, each type of seeds was pressed and squeezed separately in room temperature at the same market, after that, the produced oils were filtered for several times to remove any precipitations until they became almost pure. Subsequently, the oils were mixed in the clinical lab at the Faculty of Pharmacy, Cairo University with a ratio of one to one and put in dark bottles with graduated droppers for use.

The trial started at August 2022 when the researcher started enrollment process through daily attendance at the outpatient clinic to recruit eligible patients with CRS, however, some participants were followed up by the researcher before recruitment till the Computed Tomography (CT) scan was performed in order to confirm the diagnosis. After that, the aim of the trial was explained and each eligible participant was asked to sign the consent form. Then, demographic and medical data was collected. Afterwards, initial assessment was done for all participants in both groups regarding; severity of symptoms

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using SNOT-22 and patient satisfaction with the standard treatment using Treatment Satisfaction Questionnaire for Medication. Consequently, each participant was simple randomly allocated by the researcher into either the study or control group using opaque sealed envelopes reflecting the type of the group where each participant was asked to choose an envelope. The participants who were allocated to the study group were subjected to a sensitivity test through applying two drops of the prepared N. sativa nasal oil drops on a band aid and fixed to the participants' skin of inner forearm [26]. The researcher then instructed the participant to leave the patch in place for 24 hours, but if the participant felt any of these symptoms: itching, hotness or any reaction at the test site before or during 24 hours, the participant was instructed to remove the patch right away and report to the researcher. Based on the sensitivity test, participants in the study group were informed to follow the following steps each time using the prepared N. sativa nasal oil drops: (a) blow nose gently, (b) lie on bed with the head hanging back, (c) open the container and fill the dropper with the exact amount of oil, (d) drop one drip of the oil in each nostril, (e) stay in the described position for two minutes before getting up and (e) repeat the steps twice daily for four consecutive weeks. An illustrated flyer was given to each participant to guide the proper use of N. sativa. Furthermore, all trial's participants were advised to continue using the standard treatment as prescribed by the physician.

Upon completion of the four weeks' intervention period, each participant in the study group was instructed not to use the prepared oil or any other alternative oil for a month and continue with the standard treatment only. This was assured through supplying each participant with the exact amount of oil that covered only the intervention period. On the other hand, participants in the control group were instructed as well not to use any additional treatment aside from that prescribed by the physician. Participants were followed up via phone or the WhatsApp application to answer and/or clarify any inquiry they had. All participants were monitored and the outcomes were assessed at fixed points as mentioned in figure 1, where, the second assessment (during intervention assessment) was conducted at the second week from the trial. Otherwise, the third assessment/post-intervention assessment was carried out upon completion of the intervention, i.e., at the end of the fourth week considering that this was the time to evaluate the main research outcomes. Nonetheless, all participants were followed-up by the researcher for another additional month after the completion of the intervention period to evaluate the long term impact of the oil and the sustainability of the outcomes. During this month, the fourth (the first follow-up post-intervention) and fifth (second follow-up post-intervention) assessments were done at the sixth and eighth weeks respectively. The process of data collection ended at May 2023.

2.7 Statistical Analysis

The collected data was managed using statistical package for the social sciences (SPSS) program version 20 [27]. Descriptive as well as inferential statistics such as independent t test and Mann Whitney U test were used to test the hypotheses. Furthermore, effect size was calculated using relative risk (RR). Data was analyzed according to intention to treat analysis (ITT). Moreover, the alpha level of 0.05 was adopted to test all hypotheses.

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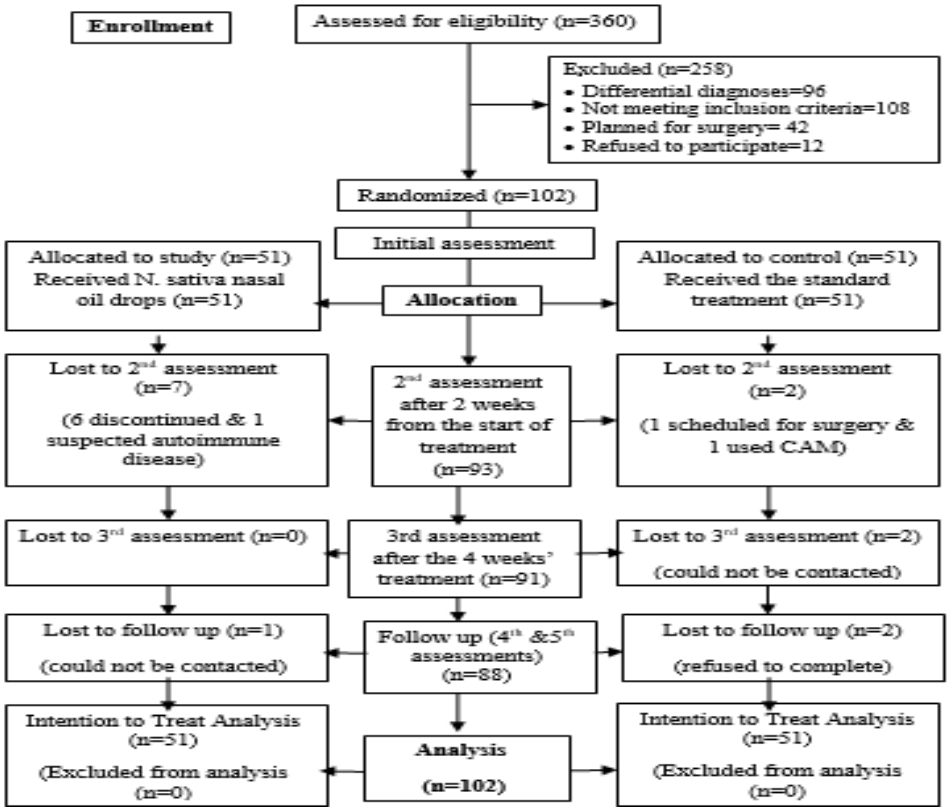

Fig. 1: CONSORT flow chart showing the main steps for the trial

3. RESULTS

Although eight and six participants did not complete the trial in the study and control groups respectively as clarified in figure 1, all the 102 participants were analyzed for both the primary and secondary outcomes (51 in each group).

3.1 Description of Participants

Table 1 presents a comparison between the study and control groups on demographic characteristics. As shown, there were no statistical significant differences between both groups regarding demographic variables. Furthermore, the participants were predominantly married, women with mean age of 39.9 ± 10.2 years. Over and above, about two thirds of the participants from each group are living in urban areas with constant exposure to allergic agents. Likewise, the minority of participants are smokers and more than half of them have been exposed to passive smoking.

On the other hand, Chi square test in table 2 revealed that there are no statistical significant differences between both groups regarding the reported chief complaints, history of using CAM and the presence of comorbidities. Further, facial pain/pressure followed by nasal obstruction were the most recurrent chief complaints among the participants in both groups.

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Table 1: Comparison between the Study and the Control Group Regarding Demographic Characteristics (N= 102)

Variables	Study group		Control group		χ^2	p value
	N	%	N	%		
Age/years						
18-	16	31.4%	22	43.1%		
31-	25	49%	14	27.5%	5.72	0.126
41-	5	9.8%	10	19.6%		
51-60	5	9.8%	5	9.8%		
	$\bar{X}$ ± SD = 39.9 ± 10.2 years					
Gender						
Male	17	33.3%	14	27.5%	0.42	0.518
Female	34	66.7%	37	72.5%		
Marital status						
Single	9	17.6%	11	21.6%		
Married	40	78.4%	36	70.6%	3.21	0.360
Divorced	1	2%	4	7.8%		
Widowed	1	2%	0	0%		
Educational level						
Cannot read or write	3	5.9%	5	9.8%		
Can rea\d and write	3	5.9%	4	7.8%		
Primary	10	19.6%	14	27.5%	3.64	0.602
Secondary	21	41.2%	21	41.2%		
Bachelor	12	23.5%	6	11.8%		
Postgraduate	2	3.9%	1	2%		
Employment status						
Employed	24	47.1%	20	39.2%	0.64	0.424
Unemployed	27	52.9%	31	60.8%		
Residence						
Rural	17	33.3%	17	33.3%	0.00	1.00
Urban	34	66.7%	34	66.7%		
Exposure to allergic agents						
No exposure	1	2%	1	2%		
1-3 agents	34	66.7%	36	70.6%	1.67	0.643
4-6 agents	15	29.4%	11	21.6%		
7-9 agents	1	2%	3	5.9%		
	$\bar{X}$ ± SD = 2.87 ± 1.73					
Smoking history	7	13.7%	8	15.7%	3.35	0.341
Negative smoking	30	58.8%	27	52.9%	0.36	0.55

Table 2: Comparison between the Study and the Control Group Regarding Medical Data (N= 102)

Variables	Study group		Control group		χ^2	p value
	n	%	n	%		
Chief complaint[a]						
-Mucopurulent drainage	19	37.3%	22	43.1%	0.37	0.545
-Cough	6	11.8%	3	5.9%	1.1	0.295
-Nasal obstruction	26	51%	28	54.9%	0.16	0.692
-Facial pain/pressure/ fullness	34	66.7%	28	54.9%	1.48	0.224
-Decreased sense of smell	13	25.5%	9	17.6%	0.93	0.336
-Others	22	43.1%	20	39.2%	0.16	0.687
Comorbidities	17	33.3%	18	35.3%	0.04	0.835
History with CAM[b]	10	19.6%	7	13.7%	0.64	0.425

[a] *Total is different from the total number of participants as more than one response was given by each participant.*

[b] *Complementary and Alternative Medicine.*

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3.2 Tests of Hypotheses

Table 3: Comparison F Total Mean Scores of the Severity of Symptoms between the Study and the Control Groups at Different Points of Assessment (N= 102)

Time of assessment	Study group (n=51) $\bar{X} \pm SD$	Control group (n=51) $\bar{X} \pm SD$	t	p value	CI[a] Lower	CI[a] Upper
Pre-intervention	67.51±20.07	71.43±19.69	-0.75	0.454	-0.15	0.07
During intervention[b]	45.98 ± 31.43	63.31±25.81	-2.86	0.005**	-0.26	-0.05
	Mean difference = -17.33					
Post-intervention[c]	38.71±36.1	64.65±27.91	-3.89	0.000**	-0.3	-0.1
	Mean difference = -25.94					
First follow-up post-intervention[d]	38.39±39.39	63.92±33.69	-3.57	0.001**	-0.29	-0.08
	Mean difference = -25.53					
Second follow-up post-intervention[e]	37.8±37.47	65.04±32.22	-4.25	0.000**	-0.31	-0.11
	Mean difference= -27.24					

[a] Confidence Interval, [b] Two weeks after starting the treatment, [c] Upon completion of the four weeks' treatment period, d Two weeks after stopping the treatment, e Four weeks after stopping the treatment.

*** p ≤ 0.01*

Table 3 shows that there are no statistical significant differences in the total mean scores of severity of symptoms between the two groups at the pre-intervention assessment (t = 0.75, p = 0.454). However, after implementing the trial, there are statistical significant differences between both groups during intervention, post-intervention and at the first as well as the second follow-up post-intervention assessments in favor of the study group (p ≤ 0.005). Therefore, the first hypothesis was supported.

Based on the findings related the first hypothesis, table 4 compares between both groups in terms of the main primary outcomes which were identified as the highest ranked severe and recurrent physical adverse signs and symptoms of chronic rhinosinusitis. The table shows that there are no statistical significant differences between both groups regarding the mean ranks of nasal obstruction/congestion, postnasal discharge and facial pain/pressure at pre-intervention assessment, while, there are significant differences between both groups at post intervention assessment in favor of the study group, where the relative risk (RR) for nasal obstruction was 0.70 and 95% Confidence Interval (CI) 0.48 to 1.04, RR for postnasal discharge was 0.48 and 95% CI 0.32 to 0.7 and RR for facial pain/fullness/pressure was 0.42 and 95% CI 0.26 to 0.69.

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Table 4: Comparison of Common Physical Adverse Signs and Symptoms (Primary Outcomes) of CRS between the Study and the Control Group at Pre/Post Intervention Assessments (N= 102)

Symptoms	Study group (n=51 $\bar{X} \pm SD$	Control group (n=51) $\bar{X} \pm SD$	Mann-Whitney U	p value	CI[a] Lower	CI[a] Upper
Nasal obstruction						
Pre-intervention	3.33±1.62	3.59±1.75	1137.5	.255	0.00	0.95
Post-intervention	2.12±1.77	3.18±1.97	908.5	.007**	0.00	0.95
Postnasal discharge						
Pre-intervention	3.37±1.71	3.71±1.55	1161.5	.332	0.00	0.95
Post-intervention	2.08±1.87	3.63±1.59	718	.000**	0.00	0.95
Facial pain						
Pre-intervention	3.43±1.64	3.9±1.43	1081.5	.122	0.00	0.95
Post-intervention	1.53±1.94	2.92±1.87	803	.001**	0.00	0.95

[a] *Confidence Interval*

*** p ≤ 0.01*

Table 5: Comparison of Common Complications of CRS (Secondary Outcomes) Between the Study and the Control Groups at Pre/Post Intervention Assessment (N= 102)

Symptoms	Study group (n=51 $\bar{X} \pm SD$	Control group (n=51) $\bar{X} \pm SD$	Mann-Whitney U	p value	CI[a] Lower	CI[a] Upper
Fatigue						
Pre-intervention	3.84±1.48	3.98±1.23	1273.5	.848	0.05	1.00
Post-intervention	2.12±2.01	3.53±1.52	793	.001**	0.00	0.95
Reduced productivity						
Pre-intervention	2.37±1.57	3.57±1.47	1212	.541	0.05	1.00
Post-intervention	1.65±1.99	3.18±1.65	749.5	.000**	0.00	0.95
Reduced concentration						
Pre-intervention	3.45±1.47	3.51±1.67	1221.5	.584	0.05	1.00
Post-intervention	1.86±2	3.27±1.83	805	.001**	0.00	0.95
Frustration/restlessness/irritability						
Pre-intervention	3.78±1.55	4.22±1.36	1067.5	.081	0.00	0.95
Post-intervention	1.98±2.04	3.49±1.71	781	.000**	0.00	0.95
Sadness						
Pre-intervention	3.35±1.84	3.65±1.66	1196	.464	0.05	1.00
Post-intervention	1.94±1.98	3.24±1.85	842	.002**	0.00	0.95

[a] *Confidence Interval*

*** p ≤ 0.01*

Table 5 compares also between both groups regarding the common complications of CRS as shown within sleep and emotional severity of symptoms' domains of SNOT-22 that represented the main trial's secondary outcomes. The table clarifies that there are no statistical significant differences between both groups regarding the mean ranks of these complications at pre-intervention assessment. However, at the post-intervention assessment, there are statistical significant differences between the two groups regarding

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the mean ranks of the common complications of CRS in favor of the study group, where RR for fatigue was .58 and 95% CI .41 to .80; RR for reduced productivity was .44 and 95% CI .29 to .66; RR for reduced concentration .53 and 95% CI .36 to .79; RR for frustration/restlessness/irritability .50 and 95% CI .35 to .72, in addition, RR for sadness .57 and 95% CI .39 to .82.

Table 6: Comparison of Total Mean Scores of Satisfaction with the Treatment between the Study and the Control Groups at Different Points of Assessment (N= 102)

Time of assessment	Study group (n=51) $\bar{X} \pm SD$	Control group (n=51) $\bar{X} \pm SD$	t	p value	CI[a] Lower	CI[a] Upper
Effectiveness						
Pre-intervention	40.85±26.66	47.17±24.65	-1.11	0.270	-0.17	0.05
During intervention	64.49±30.21	49.13±26.51	3.28	0.001**	0.07	0.27
Post-intervention	66.67±32.47	44.12±29.55	3.95	0.000**	0.1	0.29
First follow-up post-intervention	66.88±34.21	42.8±30.07	4.10	0.000**	0.1	0.3
Second follow-up post-intervention	66.45±34.5	43.03±32.01	3.95	0.000**	0.1	.0.3
Side-effects						
Pre-intervention	68.14±37.09	66.91±41.91	0.07	0.945	-0.08	-0.09
During intervention	83.70±31.35	71.32±40.3	1.84	0.069	-0.01	0.13
Post-intervention	86.15±25.35	71.45±40.7	1.99	0.050*	0.00	0.14
First follow-up post-intervention	94.98±10.31	65.56±43.36	3.89	0.000**	0.06	0.19
Second follow-up post intervention	91.79±16.98	68.01±42.68	3.28	0.002**	0.04	0.17
Convenience						
Pre-intervention	50.11±25.45	53.59±25.79	-0.78	0.437	-0.16	0.07
During intervention	69.28±24.07	56.43±23.66	3.02	0.003**	0.06	0.26
Post-intervention	70.91±26.84	54.86±27.02	3.44	0.001**	0.08	0.28
First follow-up post-intervention	72.98±26.97	50±30.14	4.15	0.000**	0.11	0.31
Second follow-up post intervention	73.2±28.52	51.63±31.75	4.15	0.000**	0.11	0.31
Global satisfaction						
Pre-intervention	45.1±27.87	43.42±27.81	-0.41	0.684	-0.09	0.13
During intervention	70.73±26.89	48.74±30.6	4.17	0.000**	0.11	0.31
Post-intervention	72.55±32.18	47.34±29.52	4.83	0.000**	0.14	0.32
First follow-up post-intervention	74.37±30.41	46.08±31.54	5.16	0.000**	0.15	0.33
Second follow-up post intervention	73.81±30.86	44.4±32.84	5.19	0.000**	0.15	0.33

[a] Confidence Interval

** $\underline{p} \leq 0.01$

Table 6 demonstrates a comparison between the two groups regarding satisfaction with the treatment as measured by Treatment Satisfaction Questionnaire for Medications. As it can be seen in the table there are no statistical significant differences between both groups at the pre-intervention assessment in all domains of treatment satisfaction. Nevertheless, there are statistical significant differences between mean total scores of satisfaction with effectiveness, convenience and global satisfaction with the treatment in favor of the study group at during intervention assessment. Further, at post intervention and first as well as second follow-up post-intervention assessment, there are significant differences between both groups in terms of all treatment satisfaction domains in favor of

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the study group. Therefore, the second hypothesis was supported, where RR for dissatisfaction with treatment effectiveness was .61 and 95% CI .46 to .81; RR for dissatisfaction with burden associated with treatment side-effects was .34 and 95% CI .20 to .61; RR for dissatisfaction with treatment convenience was .61 and 95% CI was .43 to .85; finally, RR for global dissatisfaction with treatment was .51 and 95% CI was .35 to .74.

4. DISCUSSION

The findings of the current clinical trial have empirically proven that the severity of symptoms and patients' satisfaction among patients with CRS who used N. sativa nasal oil drops for four consecutive weeks were different from the severity of symptoms and patients' satisfaction among the control group in favor of the study group. Statistical analyses of the data revealed that the former differences were related to nasal, otologic, sleep and emotional symptoms' domains. Furthermore, the primary outcomes were nasal obstruction, postnasal discharge and facial pain/pressure, while fatigue, reduced productivity, reduced concentration, frustration/restlessness/irritability and sadness surfaced as secondary outcomes.

The findings of the present trial are in harmony with a former study which reported that a total daily dose of one gram of N. sativa oil in the form of nasal spray for eight weeks was safely effective in reducing the symptoms of CRS compared to sodium chloride as a placebo [20]. The results of the current trial could be interpreted in light of the findings of an earlier animal study entitled "The value of Nigella sativa in the treatment of experimentally induced rhinosinusitis" which showed that N. sativa has an antibiotic like effect on chronic rhinosinusitis in the form of reducing sinuses' inflammation by decreasing nitric oxide level and lowering neutrophil infiltration in the sinuses [28].

Moreover, the findings of the current trial are in agreement with the results of a recent study which revealed the effectiveness of nasal drops of N. sativa oil in Sesame oil for four weeks on subjective symptoms as well as objective signs through nasal endoscopic examination. Indeed, the study concluded the effectiveness of N. sativa on improving facial pain or pressure, facial congestion or fullness, nasal congestion or obstruction, pus or nasal discharge and bad breath, in addition, the endoscopic examination showed decreased nasal inflammation, muco-purulent drainage and polyposis [21]. The current trial's results are in harmony also with the results of a trial entitled "Single-blind, randomized, control trial of a Unani compound formulation in iltehab tajaweefe anaf muzmin" which disclosed that the use of two daily doses of six grams from Unani formulations (a mixture of Linum usitatissimum Linn, Piper nigrum and Honey in the form of oral tablets) as well as steam inhalation of N. sativa pounded in water for ten minutes were effective in improving both major and minor symptoms of chronic rhinosinusitis. This improvement was interpreted as a result of the anti-histaminic effect of N. sativa [22]. Moreover, the findings of this trial was in line with a study that tested the effect of three daily doses of a semisolid mixture involving four ingredients that included N. sativa, Curcuma zedoaria, Myristica fragrans and honey on the symptoms of CRS against the

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standard antihistamine. The results showed fewer symptoms of CRS, including rhinorrhoea, sneezing, facial pain, nasal obstruction, post nasal discharge and thick nasal discharge. Researchers attributed these findings to the deobstruent, anti-inflammatory, concoctive, analgesic, expectorants and antimicrobial activities of the mixture [18].

The statistical analysis of the second hypothesis in the current trial indicated that there are no statistical significant differences between the two groups regarding patients' satisfaction with the standard treatment at the start of the trial, however, results revealed differences between both groups after receiving the assigned intervention in favor of the study group. The improvement of symptoms among the participants in the study group compared to the control group may be the reason for the improvement in patients' satisfaction. The researcher's explanation is consistent with a study, which reported that patients with CRS who had higher scores of severity of symptoms had also lower scores of satisfaction with treatment [16]. Although there are few clinical trials that investigated the patients with CRS' satisfaction with N. sativa, yet, most of the conducted studies concluded that N. sativa improved symptoms of CRS with no reported side-effects [20], [21]. Over and above, further studies confirmed the safety and endurability of N. sativa as a natural product as evidenced by the stability of liver and kidney function tests before and after the study [18], [19], [20], [21], [22].

The findings of the current trial are further congruent with a study entitled "Efficacy and safety of oral Nigella sativa oil for symptomatic treatment of knee osteoarthritis: A double-blind, randomized, placebo-controlled clinical trial" which revealed that patients with knee osteoarthritis were more satisfied with N. sativa than the placebo on 11-point visual analog scale (VAS). The study informed also that in addition to the effectiveness of N. sativa, it did not cause any side-effects either subjectively as reported by patients or objectively as determined by the stability of values of blood parameters [29].

Also the results proclaimed by the current trial are in agreement with an early study entitled "The effectiveness of Nigella sativa, methotrexate and their combination in the treatment of moderate to severe psoriasis" which reported that 80% of patients who used N. sativa only were highly satisfied with the treatment and reported no side-effects compared to only 15% and 40% in the other two groups who used the standard treatment alone or standard treatment beside N. sativa [30]. Although the aim and methods of the former studies were different from the aim and methods of the current trial, they all are highly matched in that patients are more satisfied with N. sativa than the standard treatment. To sum up, the current trial has proven the positive effects of N. sativa on severity of symptoms and patients' satisfaction when compared to a control group. These results are congruent with the previous trials, accordingly, N. sativa could be integrated with the standard treatment to control symptoms of CRS which consequently could improve patients' satisfaction. This improvement hopefully would be reflected positively on patients' quality of life by decreasing the symptoms that impact daily activities and work, hence, the number of sick leaves decreases and work days' increase, leading to better production of the society as a whole. Also, the cost related to the continuous use and consumption of medications will decrease, and this will be reflected in the economic

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situation of the individuals and society as a whole. Moreover, reducing the use of these medications, such as antibiotics and corticosteroids for these conditions may lead to reduction in side-effects which interfere with the patient's health and quality of life. In addition, the utilization of health system by these patients may decrease as they have a convenient, safe and effective self-management method for controlling the disease.

5. CONCLUSION AND RECOMMENDATIONS

It can be concluded from the current trial that the instillation of N. sativa nasal oil drops with a daily dose of 100 mg of a pure N. sativa (one drip in each nostril) had a significant effect in alleviating symptoms of CRS and improving patients' satisfaction with the treatment. Accordingly, N. sativa nasal oil drops could be integrated in treatment protocols for chronic rhinosinusitis. Also, raising awareness among health care providers about the effect and proper use of N. sativa for managing the symptoms of CRS is recommended. Last but not least, duplicating the trial on other patients with larger sample in different setting is recommended for generalizing the results.

6. LIMITATIONS

Although every effort was made to conduct this trial as described in the protocol, inevitably certain limitations existed. Some were beyond control of the researcher and some simply were over sighted. The limitations of the trial were as follows:

- The researcher planned to utilize single-blinding but it was not feasible as both treatments were physically different and most of the patients know well the standard treatment and the introduction of any other treatment will be evident to them.
- The findings are limited in generalizability due to the fact that the sample was selected from a single geographical area in Egypt.
- Some during and post-intervention assessments were conducted for several patients through telephone calls as they have difficulty keeping outpatient clinic appointments.

7. ABBREVIATIONS

CRS	Chronic Rhinosinusitis
Qol	Quality of Life
CAM	Complementary and Alternative Medicine
N. sativa	Nigella sativa
ENT	Ear, Nose and Throat
DMDF	Demographic and Medical Data Form
SNOT-22	Sino-Nasal Outcome Test 22
TSQM	Treatment Satisfaction Questionnaire for Medications
CT	Computed Tomography
SPSS	Statistical Package for the Social Sciences
RR	Relative Risk
ITT	Intension To Treat
CI	Confidence Interval
VAS	Visual Analog Scale

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8. DECLARATIONS

8.1 Ethical Considerations

This study was part of a Doctorate thesis, approved by the Research Ethics Committee of Faculty of Nursing, Cairo University (ethics code: RHDIRB2019041701). Also the study was registered on ClinicalTrials.gov (NCT05494164). In addition, a written informed consent was obtained from all participants after explaining the nature, purpose and significance of the trial as well as the expected benefit and/or risk. It was emphasized also that participation in the trial is entirely voluntary and they have the right to withdraw from the trial at any point without penalty.

8.2 Availability of data and materials

The data that support the findings of this trial are available from the corresponding author upon reasonable request.

8.3 Competing Interests

The authors declare that they have no competing interests.

8.4 Funding

This trial received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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