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Comparison of the Effect of Topical Use of *Nigella Sativa* Oil and Diclofenac Gel on Osteoarthritis Pain in Older People: A Randomized, Double-blind, Clinical Trial

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Abstract

Osteoarthritis is one of the most common diseases in the elderly. Herbal remedies create pain relief with appropriate clinical effects and less toxicity. We aimed to investigate the effect of *Nigella sativa* oil compared with diclofenac gel on the reduction of osteoarthritis pain in older people. This was a double-blind clinical trial. Samples were 52 men and women aged 60-80 years. They were selected using a convenience method, that were randomly assigned into *Nigella sativa* oil and diclofenac gel groups. The topical application of *Nigella sativa* oil and diclofenac gel was performed twice a day in the morning and night for 21 days. The Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire was used for data collection about pain before the use of drugs, in the tenth day and the twenty-first day of the intervention. Paired t-test showed that both interventions improved pain in the subjects ($P<0.05$). However, t-test and Mann-Whitney U test

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showed that pain on the 21st day after the intervention was significantly lower in the *Nigella sativa* oil group compared with that of the diclofenac gel group (P=0.04). Also, the results of this study showed that *Nigella sativa* oil had a better pain relief effect than diclofenac gel. The mean pain scores in the *Nigella sativa* oil and diclofenac gel groups before the intervention were 75±16.29 and 57.66±19.66, respectively. Also, pain on the 21st day after the intervention was 38.88±17.84 and 50.33±20.38, respectively. In general, *Nigella sativa* oil was more effective than diclofenac gel on osteoarthritis pain.

Keywords: *Nigella sativa* oil, Older people, Knee joint, Osteoarthritis, Pain, Diclofenac gel

1. Introduction

The aging population of the world is on the increase, and demographic data estimate that by the year 2050, people over 65 years will reach 22% (Lenander, 2017). Osteoarthritis (OA) is a common disease that often begins in old age (Bhandarkar et al, 2017) and is the most common form of arthritis (Zambon et al., 2016). About 40% of individuals over 70 years suffer from knee osteoarthritis (Alipour et al., 2017). This disease is the primary cause of disability in the recent reports of the World Health Organization (WHO). Also, by the year 2020, it would be the fourth cause of the world's physical disability, as 28% of the world's elderly population may suffer from it (Thomas et al, 2017).

Osteoarthritis is typically characterized by joint pain, stiffness and movement constraints, occasional effusion, and degrees of joint inflammation (Castrogiovanni & Musumeci, 2016). For the treatment of knee OA, the main goal is to reduce pain and symptoms and, if possible, reduce its progress (Capel et al., 2014). There is no standard treatment for OA. Drug therapy, however, includes analgesics, anti-inflammatory drugs, corticosteroids, glucosamine sulfate, chondroitin sulfate, and some unscientific treatments. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common drugs for OA (Tsai et al., 2014). Patients should be cautious about the side effects of NSAIDs including gastrointestinal bleeding, decreased kidney function, hypertension,

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and cardiovascular diseases (Sinusas, 2012). More serious consequences may include high blood pressure, obesity, and reduction of daily activities especially in elderly people (Breivik, 2017). The mechanism of action of NSAIDs is the blocking of prostanoids (prostaglandins, prostacyclin, and thromboxane), and prevention of prostaglandin synthesis (Angiolillo & Weisman, 2017).

In chronic conditions, especially in elderly people who suffer from OA, the oral form of these drugs is used regularly to relieve pain. The topical application of these drugs has also shown better tolerance and effectiveness than the oral use. According to international guidelines, the topical application has been recommended prior to any oral use. However, long-term topical use of these drugs may have harmful effects including gastrointestinal hemorrhage, stomach ulcer, and cardiovascular and kidney complications (Hagen & Baker, 2017). As a result, long-term administration of these drugs, especially in those patients suffering from increased arterial blood pressure, congestive heart failure, and coronary artery diseases, should be managed and the treatment period should be limited and minimized based on the patients' clinical conditions (Varga et al, 2017). Therefore, interventions for the treatment of OA should have the characteristics of the highest adherence and maximum compliance to the therapeutic regimen (Roos & Arden, 2016). In addition, poly-pharmacy among elderly people may lead to increased reactions and side effects (Breivik, 2017).

It is said that herbal medicines have no side effects and have been used for 2000 years to treat articular diseases (Tsai et al., 2014). They were the most basic methods for dealing with diseases and relieving pain. Also, due to the presence of natural substances and biological agents, they do not lead to the accumulation of drug substances in the body. Lack of side effects of herbal medicines in recent decades has attracted the attention of researchers to these drugs worldwide (Nasri, 2011) and led to effective clinical satisfaction associated with lower toxicities (Ijaz et al., 2017). One of the most commonly used herbal medicines is *Nigella sativa* oil or Shuniz, from the Alaël family commonly known as black seed in traditional medicine. The biological and pharmacological effects of this plant are attributed to thymoquinone and oil (Hussain & Hussain, 2016). The unsaturated fatty acids in *Nigella sativa* such as oleic acid can relieve pain through inhibiting the activity of the cyclooxygenase enzyme (Huseini et al, 2016). In addition, thymoquinone inhibits arachidonic metabolism through the cyclooxygenase and 5-lipoxygenase

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pathway. The cyclooxygenase enzyme converts arachidonic acid to prostaglandin H2, a progenitor of other prostaglandins, which can relieve pain (Khan & Afzal, 2016). Several studies have been carried out on the therapeutic doses of *Nigella sativa* and thymoquinone indicating their low toxicity and high safety (Amin & Hosseinzadeh, 2016). Considering the importance of the use of medicinal plant oils, in particular *Nigella sativa* oil, as a complementary treatment, the side effects of NSAIDs such as diclofenac for elderly people, and the analgesic effects of *Nigella sativa* oil in previous studies, this study aimed to investigate the effect of *Nigella sativa* oil compared with diclofenac gel on the reduction of pain due to knee OA in elderly people.

2. Materials and methods

2.1.Research design

This double-blind, parallel, clinical trial was conducted in August and September 2017 on elderly people admitted to the Health Center of Traditional Medicine affiliated to Sabzevar University of Medical Sciences, Sabzevar, Iran. The Ethics Committee of Sabzevar University of Medical Sciences approved the study protocol (ethical code: IR.MEDSAB.REC.1396.47). The study was also registered at the Iranian Registry for Clinical Trial (IRCT No: IRCT2017080835563N1). Written informed consent was obtained from all participants prior to their enrollment.

2.2.Subjects

The sample size was calculated using Kooshki and co-workers' study (2016). Confidence level of 95%, the test power of 80%, the variance (σ^2) of 0.3, the number of repetitions (m) of 3, the internal data correlation (ρ) of 0.7, and the approximate accuracy (d^2) of 0.5 were considered in the calculation. Considering power=80% (b=0.20) and α=0.05, the required sample size for detecting any difference between the groups was 23 patients in each group. However, 52 individuals were recruited to compensate the probability of a 10% dropout. In this study, two patients were excluded because of poor cooperation (one from *Nigella sativa* oil group and the other from diclofenac gel group). Therefore, data were collected from 50 elderly patients (figure 1).

$$n = {2\left(z_{1-\alpha} + z_{1-\beta}\right)^2 \sigma^2\{1 + (m-1)\rho\}}\Big/{m\, d^2} = \frac{2 * (1.64 + 1.28)^2 * 0.3 * \{1 + 2 * 0.7\}}{3 * 0.28} \cong 23$$

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The inclusion criteria were: diagnosis of OA according to the American College of Rheumatology criteria, age between 60-80 years, knee pain for more than two months, crepitus on motion, morning stiffness less than 30 minutes, existence of knee inflammation based on a physical examination by the physician, diagnosis of knee OA by the physician, and radiographic evidence. Exclusion criteria were: blindness and deafness, inability to communicate, any incurable disease, and the use of antipsychotics, narcotics, and corticosteroids. During the process of the study, patients who were unwilling to continue with the study, or developed any of the following conditions such as abnormal stress due to mourning a relative's death, incurable diseases, allergy to *Nigella sativa* oil and diclofenac gel, lesions on the knee, and/or use of other pain killers or irregular drug use were excluded too.

2.3.Randomization

The subjects were selected using the convenience sampling method based on the eligibility criteria. The subjects were then randomly assigned into 2 experimental groups by the permuted block randomization method. Group A (n=26) received *Nigella sativa* oil and group B (n=26) received diclofenac gel.

2.4. **Study settings**

The setting of the study was the Healthcare Center of Traditional Medicine affiliated to Sabzevar University of Medical Sciences, Iran. This center is located in an appropriate geographical location that provides a convenient access for elderly people. Also, a traditional medicine specialist and a nurse were present in the center.

2.5. **Interventions**

The data collection tools were the informed consent form, Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire, a form for collecting demographic data, and a checklist for collecting drug allergy data. Informed consent forms were signed by the elderly people after providing explanations about the aim and method of the study. The KOOS questionnaire was then filled out

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by the researcher before the intervention, on 10th day, and on the 21st day of the intervention. This was a patient-oriented questionnaire with 42 questions and had five domains regarding pain (9 questions), other symptoms (7 questions), function in daily living (ADL) (17 questions), knee related quality of life (QOL) (4 questions), Function in sport and recreation (Sport/Recreation) (5 questions). The patient's pain was evaluated according to the Knee Injury and Osteoarthritis Outcome Score (KOOS) with 9 questions (P1-P9). In each question, the pain severity including none, mild, moderate, severe and extreme pain when twisting/pivoting on knee, full straightening of the knee, full bending of the knee, walking on flat surface, going up or down the stairs, overnight pain in bed, while sitting or lying, and standing upright were scored. The method of calculating the pain score was to subtract the average number obtained from the KOOS scale (which ranged up to 100), and then divide it by four, and the obtained number showed us the mean pain degree. This questionnaire was assessed by 10 faculty members affiliated to Sabzevar University of Medical Sciences in terms of content validity (CVI=0.8). A demographic questionnaire including questions about age, sex, height, weight, body mass index (BMI), and other required variables in this study, was filled out by the researcher after the recruitment of the subjects. The allergy checklist was filled out every week by the researcher questioning the subjects.

BOSCH Digital Laboratory Scale was calibrated by the optimal calibration laboratory testing process, with 10 multiplicities, 95% confidence levels, and a reliability of more than 50% for the measurement of diclofenac consumption of 1 gram (Equivalent to 1 cc). Sartorius mechanical pipette (1000 λ=1 cc) was calibrated by an optimal calibration laboratory of the test process with 10 multiplicity measurements to measure 1 cc *Nigella sativa* oil from the laboratory pipette.

Topical diclofenac sodium gel (1%) with a dose of 60 grams from Tehran Razak company® was provided. Also, 37 cc *Nigella sativa* oil made by Ganjina Osareh of Isfahan pharmaceutical company® with Utility License Number of 104/7533/1335328 and Drug registration number of 1228208539 was provided. After obtaining informed consent and based on the inclusion and exclusion criteria, the subjects were selected. The patients were informed that they could withdraw from the study at any time without any effect on their care. They were assured that their information would remain confidential and the results of the study would be given to them, if they requested. They were asked to inform the researcher if they were taking other drugs. To prevent possible bias, a double-blind approach was used for data collection. The demographic and KOOS

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questionnaires were completed before the intervention, and 10 and 21 days after the intervention at noon with the help of the eligible co-researcher for each subject. The co-researcher, as a data collector and statistician, did not know about the allocation of participants in the two groups. The drugs were provided by the researcher to the participants along with a written description sheet as well as a verbal explanation about how to use them. Pain assessment was carried out in two groups (Both before and after intervention) 4 hours after taking the drugs at 12 o'clock.

It was advised that the drugs should be topically applied twice daily in the morning and before going to bed at night for 21 days; 1 cc on the painful knee joint for two minutes. The participants were asked not to use alternative drugs during the course of the intervention and inform the researcher, if additional drugs were required. After 10 days and 21 days of drug use, the KOOS questionnaire was completed by the researcher through one to one contact or by telephone interview. The subjects were advised to contact the researcher, if any problem or question arose.

The allergy checklist had questions in regard to the symptoms of redness, itching, burning, blisters, dyspnea, coughing, dizziness, hot flashes, and coughs, which was completed each week for 21 days during the study. None of the subjects reported any allergic reaction. During the study, other than the random assignment of the subjects to the groups, appropriate supervision on the continuity of the research process was carried out. After collecting the data, statistical analysis was performed.

2.6.Statistical analysis

Chi-square test was used to examine gender, history of dietary and exercise habits homogeneity in both groups. Fisher's exact test was also used to examine the history of osteoporosis, dietary habits and type of pain killers use. Age was compared with Mann-Whitney U nonparametric tests, and BMI in two groups was compared with student t-test. Since the pain measurement was carried out in three steps on two groups, the GEE method with the identity link function was used.

Results

The mean±SD ages of the patients in the *Nigella sativa* oil and diclofenac gel groups were 66.44±5.83 and 67±6.44 years, respectively. They had a comparable BMI. The percentages of

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female and male patients in the *Nigella sativa* oil group were 51% and 49%, respectively, and in the diclofenac group were 47% and 53%, respectively (table 1).

Chi-square test did not show any significant differences in terms of the type of analgesic drugs used between *Nigella sativa* and Diclofenac groups, and the two groups were similar (P = 0.07, table 2).

The mean scores of pain before the intervention (the first period) in the *Nigella sativa* (black cumin) oil group and the diclofenac group were 75±16.29 and 69.88±18.24, respectively (P=0.301).

The mean scores of pain on the 10th day of the intervention (the second period) in the *Nigella sativa* oil group and the diclofenac group were 54.44±17.31 and 57.66±19.66, respectively (P=0.542).

The mean score of pain on the 21st day of the intervention (the third period) in the *Nigella sativa* oil group and the diclofenac group were 38.88±27.88 and 50.33±27.88, respectively, which was statistically significant (P=0.040, figure 2).

Discussion

The results of this study showed that whilst by the 10^{th} day of the intervention in both groups, there were decreases in pain, they were not statistically significant. However, on the 21st day of the intervention, the effect of *Nigella sativa* oil on pain was higher compared with the effect of diclofenac gel. This shows the effectiveness of *Nigella sativa* oil on the reduction of pain over time. Considering that no allergic reaction was reported, *Nigella sativa* oil can be used as a safe alternative method to relieve OA pain. A few studies have been conducted on the effect of *Nigella sativa* oil on knee joint pain, especially in elderly people, however most studies have been carried out on animal species. Kooshki and colleagues (2016) investigated the effect of *Nigella sativa* oil and oral acetaminophen on pain due to knee OA. They concluded that the use of topical *Nigella sativa* oil could be more effective in reducing knee pain compared with acetaminophen pills (Kooshki et al, 2016), which was similar to our findings. In line with the results of this study, Bashir and co-workers (2015) compared the effect of *Nigella sativa* oil and diclofenac sodium on mice and showed that anti-inflammatory and anti-analgesic activity of *Nigella sativa* oil was

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greater than diclofenac gel. It also had a better efficacy in long-term use compared with chemical drugs (Bashir, Qureshi, & Saleem, 2015).

Thymoquinone seems to be one of the main ingredients of *Nigella sativa* extract that has analgesic effects and can be used in pain and inflammatory disorders. Similarly, a study by Roghani and others assessed the effect of long-term use of oral *Nigella sativa* seeds on white mice and concluded that the administration of *Nigella sativa* for two months significantly reduced the sensation of pain and could be considered as an alternative treatment in hyperalgesia. They reported that thymoquinone probably existed in this plant and was the most effective ingredient (Roghaniet al, 2006). In another study assessing the analgesic and antipyretic effects of *Nigella sativa* oil on animal model, the effect of the time of use of *Nigella sativa* oil or its long-term anti-analgesic activity was compared with other medications (Pise & Jadhav, 2016). In a human study by Hosseini and co-workers on the effects of topical *Nigella sativa* oil and diclofenac gel in the treatment of cyclic pain in the breast, the use of diclofenac gel and *Nigella sativa* oil showed significant and meaningful results in comparison with the placebo. They supported the effect of *Nigella sativa* oil on pain, which was consistent with the result of this study (Huseini et al., 2016). A study by Mirmollaie and co-workers showed a more effective anti-analgesic effect of *Nigella sativa* compared with diclofenac gel over time (Mirmolaeiet al, 2017). In another study on patients with rheumatoid arthritis, pain score was reduced by the use of *Nigella sativa* oil compared with before the study and placebo (Gheita & Kenawy, 2012), which similarly indicated the effect of *Nigella sativa* oil on the reduction of pain.

Limitations

Due to the age range of the subjects, the continuation of the intervention treatment was time consuming. Another limitation of this study was that patients were all recruited from a health center that could affect the generalizability of the findings. Polypharmacy was another limitation in this study, because it was unethical to prevent elderly people from taking their medications. Also, low sample size might have affected the power of the study. Another limitation of the current study was the lack of a third control group using massage in the knee region to evaluate the effect of massage on pain reduction, to ensure that the analgesic effects were related to the treatment not to the rubbing action related to the application of the *Nigella sativa* oil.

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Conclusion

Considering the importance of the use of medicinal plant oils, especially *Nigella sativa* oil, as a complementary therapy, and complications of NSAIDs such as diclofenac in elderly people, it is suggested that *Nigella sativa* oil can be used in elderly people who suffer from knee joint pain. The overall results showed that *Nigella sativa* oil could be substituted for diclofenac gel for the reduction of pain.

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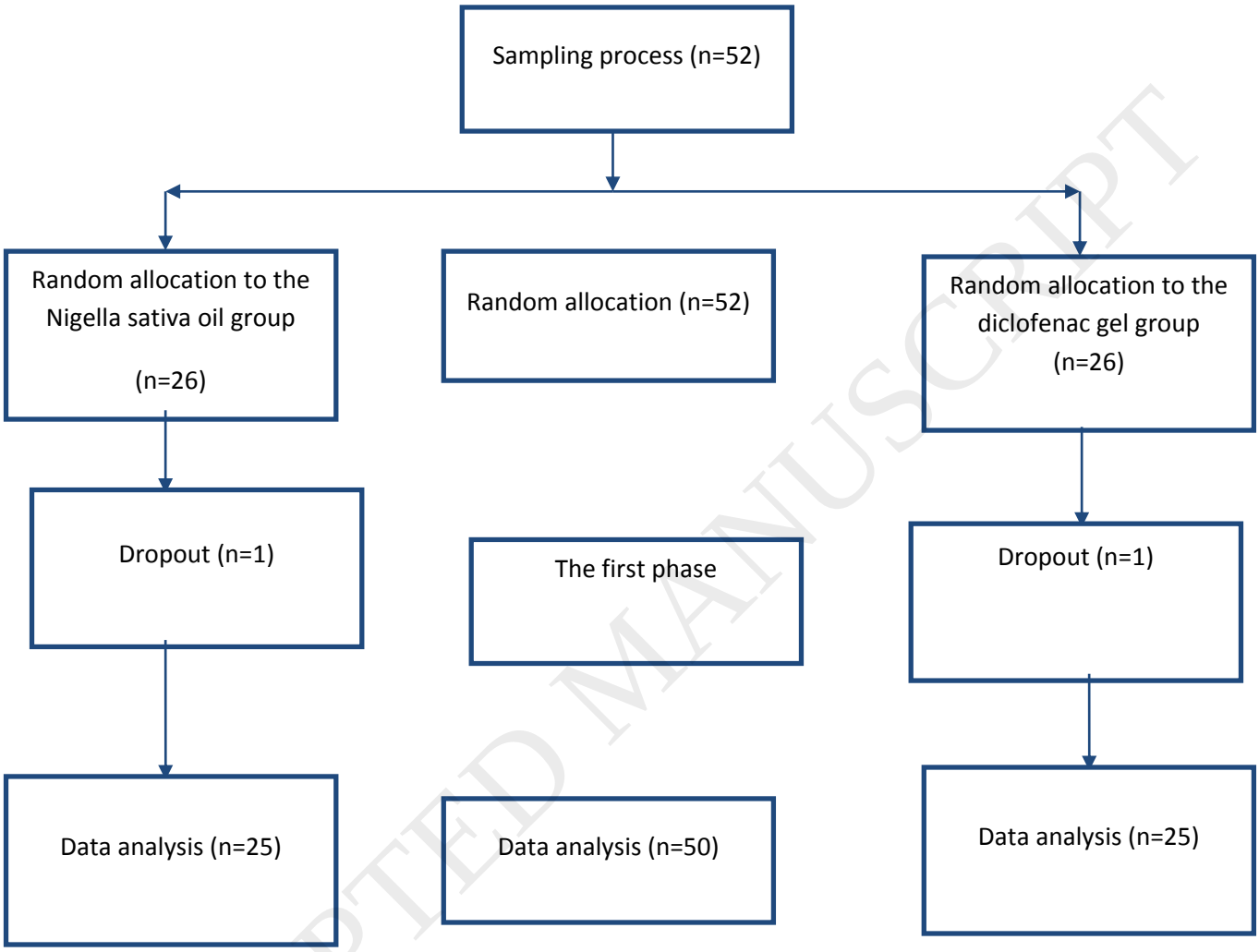

Figure **1.** Flowchart of the design, group, and participants in the study

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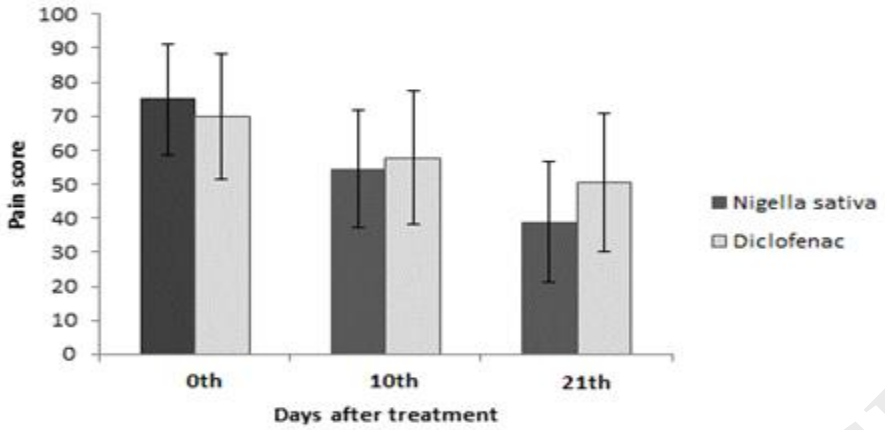

Figure 2: The score of pain in the groups (Nigella sativa and diclofenac)

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Table 1: The demographic and disease-related characteristics of the subjects in the groups

Group / Variable		*Nigella sativa* oil group	Diclofenac gel group	Pvalue	Test
		mean ±SD*	mean ± SD*		
Age		66.44±5.83	67±6.44	P=0.520 Z=-0.644	Mann-Whitney U
Body mass index		27.54±4.67	27.38±3.76	P=0.895 T=0.133	t test
		N** (%)***	N (%)		
Sex	Female	18(51.4%)	17(48.6%)	P=0.500	Chi-square (Pearson)
	Male	7(46.7%)	8(53.3%)		
Occupation	House wife	14(56%)	16(64%)	P=0.886	Chi-square (Fisher)
	Employee	1(4%)	0(0%)		
	Worker	2(8%)	1(4%)		
	Retired	6(24%)	7(28%)		
	Farmer	2(8%)	1(4%)		
History of pain killers use	Yes	20(80%)	19(76%)	P=0.500	Chi-square (Pearson)
	No	5(20%)	6(24%)		
History of Osteoporosis	Yes	14(56%)	9(36%)	P=0.128	Chi-square (Fisher)
	No	11(44%)	16(64%)		
Exercise habit	Walking	10(40%)	15(60%)	P=0.389	Chi-square (Pearson)
	No exercise	13(52%)	8(32%)		

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	Several types of activities	2(8%)	2(8%)		
Eating habit (taking dairies)	High	1(4%)	4(8%)	P=0.297	Chi-square (Fisher)
	Moderate	11(44%)	7(28%)		
	Low	13(52%)	14(56%)		

*= Standard Deviation

**= Number

***= Percent

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Table 2: Comparison of two groups (*Nigella sativa* and Diclofenac) in terms of pain killer types used by participants

Type of pain killer	*Betamethasone*	*Naproxen*	Ibuprofen	P- Value
Nigella sativa Group	1	0	1	(P=0.07)
diclofenac group	0	3	3	
Sum	1(2.6%)	3 (7.7%)	4 (10.3%)	

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