

Comparing the Effects of Sesame Oil vs. Nitroglycerin Ointment on the Incidence of Chemotherapy-Induced Phlebitis: A Single Blind Clinical Trial

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Abstract

Background: Phlebitis is a severe inflammatory response in patients undergoing chemotherapy that can lead to complications and increased length of hospitalization. **Objective:** This study was conducted to examine the effects of sesame oil and nitroglycerin ointment on the incidence of chemotherapy-induced phlebitis in patients with cancer. **Methods:** This clinical trial study involved 138 cancer patients who were randomly assigned into three groups. The three groups received nitroglycerin ointment, sesame oil, or betadine alcoholic solution that were applied on the distal catheter area at a length of 1.5 centimeters and width of 2 × 4 cm using graded paper. The site was then dressed and fixed with anti-allergenic adhesives. The research samples were examined for 72 hours for the incidence of phlebitis. **Results:** No statistically significant difference was observed between the incidence of phlebitis in the sesame oil, nitroglycerin ointment and alcohol-betadine groups in the first 24 hours (p=0.2), the second 24 hours (p=0.13) and the third 24 hours (p=0.13). **Conclusion:** External use of both sesame oil and nitroglycerin is effective in reducing chemotherapy-induced phlebitis. Due to its anti-inflammatory effect and low cost, however, using sesame oil is recommended.

Keywords: Phlebitis- nitroglycerin- sesame oil- chemotherapy- nursing

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Introduction

Cancer is a disease process that results from abnormal or acquired mutations causing abnormal cell behavior, and a set of different causes are involved with different manifestations, treatments, and prognoses (Wing and Schiffman, 2022). Chemotherapy as a cancer treatment has an important role in extending the lifespan of patients. However, chemotherapy drugs have multiple adverse effects. One of these adverse effects is phlebitis (Harris et al., 2020). Chemical phlebitis causes symptoms such as redness, erythema, pain, swelling, fever, as well as hardening and sclerosis of the vein, resulting in a palpable venous cord and thrombosis of the upper extremity veins (Bigdeli Shamloo et al., 2015, Harris et al., 2020).

Currently, pharmacological and non-pharmacological treatments are being recommended to prevent or reduce the severity of phlebitis symptoms. Therapeutic approaches such as performing chemotherapy through a port (Mosavi et al., 2020), saline lock (Eghbali-Babadi et al., 2015), topical nitroglycerin (Avaze et al., 2004), or other methods such as rapid injection and dilution

of chemotherapy agents, immediate catheter removal, heparin intermittent flushing, prophylactic antibiotics, transparent dressings, topical application of anti-inflammatory agents or corticosteroids, and application of a hot and/or wet compress (Annisa et al., 2017, Marsh et al., 2015). Herbal medicines such as sesame oil (Bigdeli Shamloo et al., 2015) and aloe vera (Sadoyu et al., 2021) are also used for this purpose. The published data shows that SO contains predominantly mono and polyunsaturated fatty acids (70–80 %) and 2–3% of unsaponifiable matter such as lignans (0.2 to 0.4 %), tocopherols, phytosterols and phenols. The health benefits of SO are associated with sesame lignans such as sesamol and sesamin, tocopherols and phytosterols due to their anti-oxidant properties. These lipophilic molecules (lignans, tocopherols and phytosterols) have been reported to be present in organic solvents (methanol, ethyl acetate, acetone, chloroform and hexane), extracts from SO, sesame seed (SS), or defatted SO (Deme et al., 2018).

However, no definitive methods have been proposed to treat and prevent chemotherapy-induced phlebitis (Kohno et al., 2015). Therefore, there is a dire need for

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appropriate, low-cost, and novel methods to prevent or alleviate the symptoms associated with chemotherapy-induced phlebitis. The present study aimed to compare the effects of nitroglycerin ointment versus sesame oil on the incidence of chemotherapy-induced phlebitis in cancer patients.

Materials and Methods

Study design

This was a single-blind randomized, controlled, parallel-group clinical trial.

Participants and setting

This study was conducted on 138 patients admitted to the oncology wards of Shaid Baghaei Hospital affiliated to Ahvaz Jundishapur University of Medical Sciences, Ahvaz, southwest of Iran, from May to October 2018. The inclusion criteria were as follows: being aged between 18-65 years old, having healthy upper extremities (absence of phlebitis), experiencing minimum hospital stay of 72 hours, having healthy and natural skin around the venipuncture site, having no history of dermatological and cardiovascular diseases, not having any combination therapies (i.e., chemotherapy in addition to radiotherapy or surgery), having no history of diabetes, vascular diseases, musculoskeletal diseases, verbal or mental disorders, autoimmunity, any signs of fever and neutropenia, allergic reactions to herbal oils, addiction to drugs or alcohol, taking no antibiotics, analgesics, and narcotics for pain relief, drugs or herbal remedies to treat phlebitis, and absence of port catheter to receive chemotherapy. The participants were excluded from the study if they: wished to withdraw from the study at any phase of the intervention for clinical or personal reasons, missed more than two follow-up sessions during the intervention, and experienced any signs of allergy to SO (sesame oil) or Nitroglycerin Ointment 2 % (NO) during the trial.

The sample size was estimated based on a recent trial (Bigdeli Shamloo et al., 2015) in which the optimal sample size was estimated to be 41 patients per group at a confidence level of 95% and power of 0.80. Finally, considering a 10% attrition rate, the sample size was determined to be 46 patients for each group.

Randomization

Due to the nature of this study, blinding of the researchers and participants was not possible. A statistician who was not involved in the study prepared a randomized allocation table. Patients were randomly assigned (1:1) to receive sesame oil, nitroglycerin ointment, or betadine alcoholic solution using randomized permuted blocks (block size 6). After randomization, the codes allocated to each participant were kept by the oncology ward clerk for preserving allocation concealment. Therefore, neither the participant nor the researcher was aware of the allocation order until the commencement of the intervention (Figure 1).

Ethical Considerations

This study was approved by the Ethics Committee of

Ahvaz Jundishapur University of Medical Sciences (Ref. ID: IR.AJUMS.REC.1396.555). Ethical considerations were observed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The study was registered in the Iranian Registry of Clinical Trials (No. IRCT20171203037737N1).

Intervention

After washing hands and wearing latex gloves, the researcher performed venipuncture on all participants. To make the intervention convenient, all catheters were placed in the anterior forearm and backside of the participants' hands. At a physician's discretion, the nitroglycerin ointment (made by Zawaira Co. in Poland) or Varuna sesame oil (made by Kimiagar Company in Kerman, Iran; with the license number of 4408 issued by Iran's Ministry of Health and Medical Education) was then applied. After aseptically prepping the site, nitroglycerin or sesame oil ointment was applied to the distal catheter area: 1.5 cm in depth and in an area of 2 x 4 cm, using a graded paper. A sterile dressing was placed on it and was secured using hypoallergenic glue. The selection of the distal catheter area is due to the fact that ointments are more likely to enter the vessels thanks to the penetration of the angiocath needle into the vessels, which increases the possibility of severe side effects of ointments, especially nitroglycerin ointment. Even the simultaneous application of nitroglycerin ointment and alcohol can cause a drop in blood pressure once every 12 hours (in a 72-hour period). In case of drug leakage into the patient's vein and presentation of symptoms of phlebitis such as pain, the patients were excluded from the study.

Data Collection

The data collection tool in this study included two sections. The first section elicited demographic information (gender, age, occupation, and education) and information about the absolute number of neutrophils, the duration of the disease, the duration of chemotherapy, and the chemotherapy regimen (type, dosage, frequency, and administration). The second section included a checklist to record the frequency of phlebitis in the first 24 hours, the second 24 hours, and the third 24 hours after the intervention.

Data Analysis

All tests were two-sided and $p < 0.05$ was considered statistically significant. The Kolmogorov-Smirnov was used to examine the normal distribution of continuous variables. Categorical data were summarized as numbers (percentages). Continuous variables were reported as mean \pm SD. Kruskal-wallis test, Chi-square and Fisher's exact tests were applied to compare study variables across the three groups. Friedman test was applied to examine the proportion of phlebitis over time in each groups.

Results

Demographic and clinical characteristics

The differences between the experimental and control groups in terms of demographic and clinical information

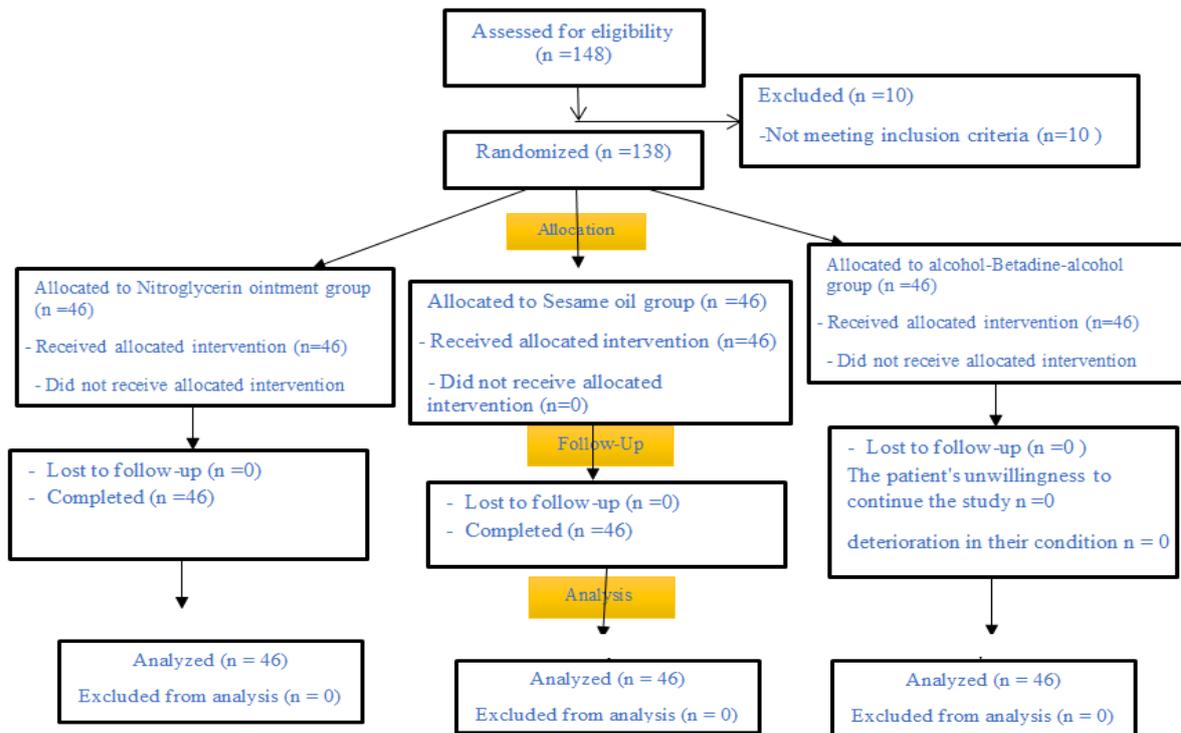


Figure 1. Consort Flowchart of Randomization

Table 1. Demographic and Medical Details of Patients in the Intervention and Control Groups

	Variable	Alcohol swabs	Nitroglycerin	Sesame oil	Total	P
	Age(year)	45.80± 15.83	47.81± 13.81	46.90±14.73	46.93±14.70	0.899 ^k
Gender	Male	29.(63.0%)	28 (60.9%)	25 (54.3%)	82 (59.4%)	0.677 ^c
	Female	17 (37.0%)	18 (39.1%)	21 (45.7%)	56 (40.6%)	
Injection location	Hand	25 (54.3%)	28 (60.9%)	22 (47.8%)	75 (54.3%)	0.454 ^c
	Forearms	21 (45.7%)	18 (39.1%)	24 (52.2%)	63 (45.7%)	

^c, Chi-square test; ^k, Kruskal-Wallis test.

are shown in Table 1. Fifty-six participants (40.6%) were female, and 82 (59.4%) were male. The age range of the participants was 46.93 ± 14.70, and most of them were aged 44-55 years old. Venipuncture was done on the backside of 75 participants' hands (54.3%) and in the forearms of 63 other participants (45.7%). The Kruskal-Wallis test results indicated no significant differences

between the three groups in terms of demographic information such as age group, gender, duration of illness, and length of hospital stay. These findings showed that diabetes (n=9; 35.5%) and hypertension (n=25; 18.11%) were more prevalent among the participants.

Results of the chi square test revealed no statistically significant difference between the incidence of

Table 2. Comparison of Phlebitis in the Groups Treated with Alcohol Swabs, Nitroglycerin Ointment and Sesame Oil

Time	Alcohol swabs		Nitroglycerin		Sesame oil		P [†]
	Number	Percent	Number	Percent	Number	Percent	
First 24 hours	3	6.5	0	0	0	0	0.04
Second 24 hours	1	2.2	1	2.2	0	0	0.6
Third 24 hours	0	0	0	0	0	0	-

[†]Chi-square test.

Pair-wise comparisons.

	First 24 hours	Second 24 hours	Third 24 hours
Alcohol-Nitroglycerin	0.242	> 0.99	-
Alcohol- Sesame oil	0.242	> 0.99	-
Nitroglycerin- Sesame oil	NA	> 0.99	-

phlebitis in the sesame oil, nitroglycerin ointment and alcohol-betadine groups in the first 24 hours ($p=0.2$), the second 24 hours ($p=0.13$) and the third 24 hours ($p=0.13$) (Table 2).

Discussion

This study showed that the use of sesame oil and nitroglycerin 2% had no positive effect on the incidence of chemotherapy-induced phlebitis. Hence, sesame oil and nitroglycerin ointment had the same effects on the chemotherapy-induced phlebitis. According to the findings, there were no significant differences between the three groups in terms of age ($P= 0.899$), and gender ($P=0.677$).

Although some phlebitis symptoms were observed in the groups treated with routine alcohol swabs and nitroglycerin ointment in the first and second 24-hour periods, no signs of phlebitis were observed in the group treated with sesame oil during the three 24-hour periods after venipuncture. However, there were no significant differences between the three groups in terms of the incidence of phlebitis.

In the first 24-hour period, three cases of phlebitis were observed in the group treated with alcohol swabs. In the second 24-hour period, one case of phlebitis was found in the group treated with alcohol swabs, and whereas one case was detected in the nitroglycerin ointment group. Nevertheless, there were no signs of phlebitis in the sesame group in all the three follow-up periods. Nor were there any significant differences between the frequency of phlebitis symptoms and the use of routine alcohol swabs, nitroglycerin ointment, or sesame oil. Although the research results indicated that there were no correlations between the severity and incidence of phlebitis in all the three studied groups during the three 24-hour periods ($P\text{-value} > 0.05$), the absence of phlebitis in the sesame oil group could exert beneficial effects on the incidence of phlebitis. Consistent with this finding, Bigdeli et al., 2015 indicated that the application of sesame oil was efficient in reducing the symptoms and severity of phlebitis in patients. Bagheri et al., 2015 also reported that the sesame oil significantly reduced the incidence of phlebitis in their studied patients. The sesame oil can protect the skin because it contains the essential fatty acids of phytosterols and antioxidants (Borchani et al., 2010). The sesame oil can also be absorbed through the skin; therefore, it plays a key role in preventing phlebitis (Shafipour et al., 2017).

Regarding the effects of nitroglycerin ointment on phlebitis, a previous study was conducted to compare the effects of clobetasol and nitroglycerin ointments on the incidence of angiocath-induced superficial phlebitis. They reported that nitroglycerin ointment reduced the catheter-induced phlebitis and recommended it to be used to prevent the incidence of phlebitis in patients requiring the long-term use of angiocath (Akbari et al., 2014). Avazeh et al., 2004 analyzed the effects of topical application of nitroglycerine on the incidence and severity of catheter-induced phlebitis. They reported the beneficial effects of nitroglycerin on phlebitis and recommended it to be used at venipuncture sites where catheters needed to

be kept for more than 48 hours (Avaze et al., 2004). The research findings showed that the effects of nitroglycerin ointment were not significantly different from those of the routine alcohol swabs and sesame oil. However, only one case of sensitivity was observed in the second 24 hours after the nitroglycerine ointment was used. This finding confirmed the results reported by Akbari et al., 2014 and Avazeh et al., 2004 with respect to the ability of nitroglycerin ointment to reduce phlebitis in patients requiring long-term catheters .

According to the literature, there has been a significant reduction in the number of patients with phlebitis after catheter insertion in recent years. This may be due to the use of new hand rap solutions on the part of nurses as well as the training and emphasis on proper hand washing procedures, which have been implemented in hospitals as a patient safety principle in recent years. Given the complications of using alcohol swabs, Betadine alcoholic solution, and nitroglycerine ointment along with the high costs of using these substances compared with sesame oil, it is recommended to use sesame oil to treat patients with skin problems. Nurses should also be encouraged to use herbal remedies to prevent or reduce the severity of chemotherapy-induced phlebitis. The use of various ointments is also suggested for the management of phlebitis. In addition, clinicians can teach the patients and their families how to use herbal medicines, especially sesame oil, as confirmed in several studies.

In conclusion, this study showed that using sesame oil, as opposed to alcohol, had a positive effect on the incidence and severity of chemotherapy phlebitis. Furthermore, sesame oil and nitroglycerin ointment left the same effects on chemotherapy phlebitis. Therefore, sesame oil can be used as a safe method to deal with chemotherapy-induced phlebitis. One limitation of this study was the small number of patients hospitalized for up to 72 hours.

Author Contribution Statement

Research conception and design: NS, NE, SM, EM and AE. Data collection: NS. Analysis and interpretation of data: NS and EM. Drafting of the manuscript: NS, NE, SM, EM and AE. Review and editing: NS, NE, SM, EM and AE. All authors contributed to the article and approved the submitted version.

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Conflict of Interest

All authors declared that there are no conflicts of interest.

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