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Effects of topical sesame (Sesamum indicum) oil on the pain severity of chemotherapy-induced phlebitis in patients with colorectal cancer: A randomized controlled trial

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ABSTRACT

Background and purpose: Chemotherapy-induced phlebitis (CIP) is one of the most important and common complications in patients with cancer. Currently, the use of complementary methods to prevent or alleviate phlebitis symptoms has attracted great attention. In this study, we aimed to assess the effects of topical sesame oil in reducing the pain severity of CIP.

Materials and methods: This randomized clinical trial was conducted on 60 patients with colorectal cancer afflicted with CIP. Patients received, twice a day for seven consecutive days, a 5-min massage solely (as the control group) or with 10 drops of sesame oil (as the experimental group) within the 10 cm radius of the affected site. The pain severity was evaluated by the visual analog scale on the first, third, fifth, and seventh days of the intervention.

Results: Mean changes of the pain severity compared to the baseline were significant on the third ($P = 0.009$), fifth ($P < 0.001$), and seventh ($P < 0.001$) days of the intervention in favor of the experimental group. Also, a significant reduction in the pain severity both in the experimental and control groups was observed during the seven days ($F = 720.66$, $P_{time} < 0.001$); however, the decrease was more significant in the experimental group ($F = 21.46$, $P_{group} < 0.001$).

Conclusion: Application of massage with sesame oil as a complementary method is effective in reducing the pain severity of patients with CIP.

1. Introduction

Chemotherapy is one of the most common and acceptable methods to manage different types of cancer [1,2]. However, most chemotherapy agents can act as a strong intravenous stimulant causing phlebitis and dysfunction in the superficial veins [3,4]. Based on recent evidence, most patients undergoing chemotherapy experience chemotherapy-induced phlebitis (CIP) associated with the presence of a peripheral venous catheter (PVC) [5–7]. Patients with this condition commonly experience erythema, vein discoloration, fever,

Abbreviations: BMI, Body mass index; CIP, Chemotherapy-induced phlebitis; Hb, Hemoglobin; MEBO, Moist exposed burn ointment; PVC, Peripheral venous catheter; SO, Sesame oil; WBC, White blood cells; VAS, Visual analog scale; VIFS, Visual infusion phlebitis scale

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inflammation, shooting pain, and edema around the injection site [8,9]. Moreover, this condition can increase the relocation and removal of the PVC [10].

Currently, different preventive and therapeutic approaches have been proposed for CIP 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 [11–15]. However, there is a lack of definitive methods to treat and prevent CIP [16–18]. Therefore, there is a great need for appropriate, low-cost, and novel methods to prevent and alleviate the symptoms associated with CIP.

In the recent decades, considerable attention has been paid to traditional herbal medicines to manage different types of phlebitis [19–25]. Recent animal and human model investigations have indicated the effects of some herbal extracts such as *Aloe vera*, *Matricaria chamomilla*, and *Xianchen* (a Chinese herb) to prevent and treat CIP [19,22,24]. One of the other herbal extracts is *Sesamum indicum*, commonly known as sesame oil (SO), which has attracted much attention in recent years to manage different types of phlebitis [2,9,18]. Recently, trials have identified the effectiveness and safety of the external application of SO to prevent and delay CIP in patients with cancer [2,18]. However, to the authors' best knowledge, no trial has yet addressed the effects of SO in reducing the symptoms of CIP including erythema, edema, pain, and inflammation. Since previous trials have indicated the analgesic activity of topical SO in other conditions [26,27], we aimed to evaluate the effects of topical application of this oil on the pain severity of CIP in patients with colorectal cancer.

2. Materials and methods

2.1. Study design

This was a randomized, non-blinded, controlled, parallel-group clinical trial. The study was registered in the Iranian Registry of Clinical Trials (No. IRCT2015041614930N2).

2.2. Patients

This study was conducted both on outpatients and inpatients admitted to the Oncology Ward of Ganjoyan Hospital, affiliated to Dezful University of Medical Sciences from June to October 2015. The inclusion criteria were as follows: 1) being in the age range of 20–60 years; 2) being conscious; 3) having the ability to read and write in Persian; 4) having at least one year history of colorectal cancer; 5) not having any combination therapies (i.e., chemotherapy in addition to radiotherapy or surgery); 6) having the experience of phlebitis symptoms in the upper extremity occurring during one to three weeks after the first chemotherapy session; 7) obtaining a score of two in the visual infusion phlebitis scale (VIFS) (Fig. 1) and a score of one to three (mild pain) in the visual analog scale (VAS) during the admission time (for outpatients) or on the first day of recruitment (for inpatients); 8) 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, and addiction to drugs or alcohol; 9) taking no antibiotics, analgesics, and narcotics for pain relief, and drugs or herbal remedies to treat phlebitis; and 10) absence of port catheter to receive chemotherapy. The exclusion criteria were as follows: 1) patient's desire to withdraw at any phase of the intervention for clinical or personal reasons; 2) absence in the follow-up sessions more than twice during the intervention; and 3) experience of any signs of allergy to SO during the trial.

The sample size was estimated based on a recent trial [9], showing a significant difference in phlebitis incidence rate between the SO group (38%) and control group (77%) at the end of the intervention ($P < 0.001$). According to the estimated proportions and using the following formula (the Pocock sample size formula for a dichotomous response [28]), the optimal sample size was estimated to be 22 patients per group at a confidence level of 95% and power of 0.80. However, 30 patients per group were selected to counteract with the dropouts.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left[p_1 (1 - p_1) + p_2 (1 - p_2)\right]}{(p_1 - p_2)^2}$$

$$= \frac{(1.96 + 0.84)^2 \left[0.38(0.62) + 0.77(0.23)\right]}{(0.38 - 0.77)^2} = 21.27 \cong 22$$

2.3. Randomization

Patients were selected using the convenience sampling method, and the ones that met the inclusion criteria were randomly allocated into two equal groups of experimental (n = 30) and control (n = 30), using the table of random numbers. Randomization was conducted by the first research assistant, the only research team member that had access to the numbers during the course of the trial.

2.4. Ethical approval

Before the commencement of the study, the Ethics Committee and the Institutional Review Board of Dezful University of Medical Sciences (Dezful, Iran) approved the study protocol (No. dur-137). All the procedures were performed in accordance with the ethical considerations of the Institutional Research Committee and based on the Declaration of Helsinki. The study methods and objectives were explained to the patients and written informed consents were obtained from all of them before enrollment. The patients were also assured of the confidentiality of their personal information and anonymity of the records. Moreover, all the patients had the right to withdraw from the trial at any time and were assured of the safety of the intervention, considering the findings of the pilot study.

2.5. Intervention

Patients in the experimental and control groups received the same care protocol for CIP by a blinded nurse (the second research assistant) under the supervision of a blinded oncologist (the third research assistant). In all the patients, new venous catheterization was performed using a 22-gauge angiocath (Medikit model, Mabna Teb Pars Co., Tehran, Iran) in the healthy upper extremity. Patients received chemotherapy during two consecutive days in a week, using the FOLFOX-4 regimen (the first day: oxaliplatin 80 mg/m^2 + leucovorin 200 mg/m^2 + 5-fluorouracil 400 mg/m^2 bolus and 600 mg/m^2 infusion, and the second day: leucovorin 200 mg/m^2 + 5-fluorouracil 100 mg/m^2 infusion). In addition, to prevent vomiting or nausea, all the patients received granisetron (10–20 μg/kg) and dexamethasone (0.3 mg/kg) dissolved in 250 mL 0.9% sodium chloride (normal saline) solution before each chemotherapy session. Moreover, patients received pethidine (50 mg/kg) as the analgesic at anytime required.

On the first day of recruitment, all the patients received training from an expert nurse (the main researcher) using the face-to-face technique during a 2 h-session in the participating ward about the intervention and the standard care of phlebitis. All the patients were advised to take only the prescribed drugs, and avoid the use of any other medications (i.e., antibiotics and pain-relief drugs) or herbal extracts without permission of the assistant oncologist. Also, the patients were asked to apply a warm compress (47 °C) on the site of phlebitis for 20 min (with 6 h intervals) on the first day of recruitment. To implement the interventions and assess the outcomes, all of the outpatients were asked to refer to the recruitment ward at the appointed time.

In the experimental group in each intervention session, 10 drops of SO (about 3 mL) was applied to the phlebitis site using a dropper. Then, 10 cm radius of the phlebitis site was massaged immediately for 5 min

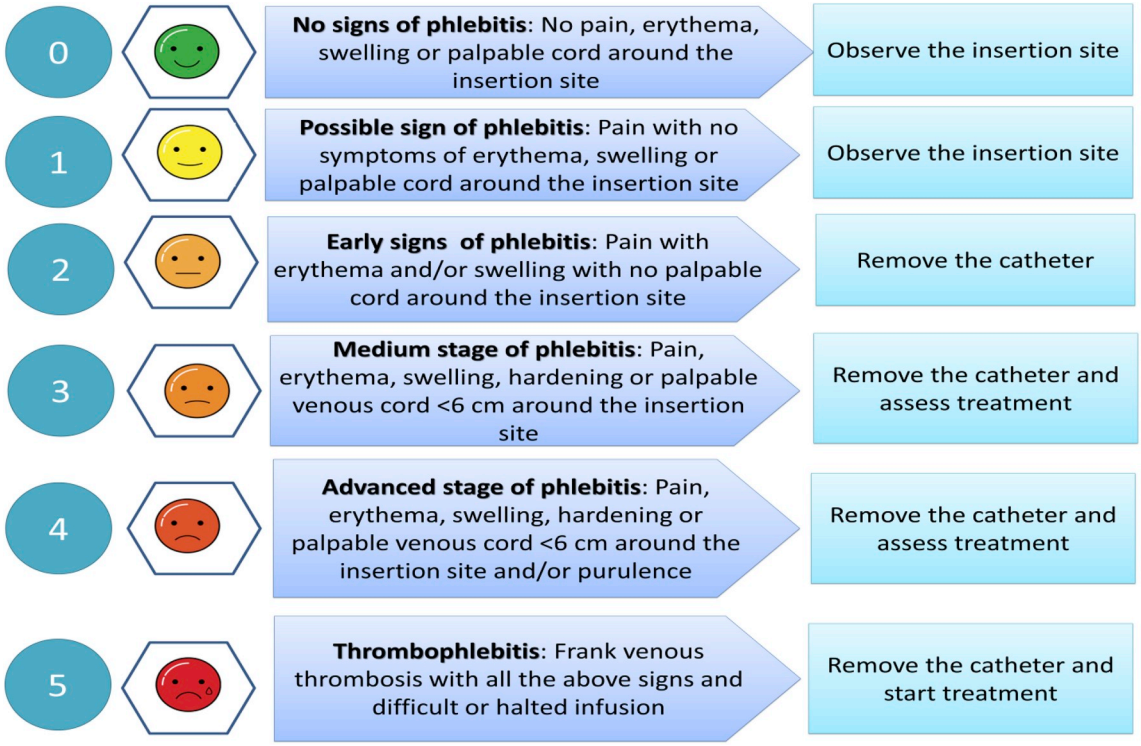

Fig. 1. The visual infusion phlebitis scale [30,31].

using a sterile gloved finger with the rotatory technique (light and gentle rubbing circular movements). Based on the opinion of the assistant pharmacologist and a previous trial [18], we used SO produced by Saman Sesame Oil Co., Tehran, Iran, with a purity of 100%, effective components of which consisted of oleic acid (43%), linoleic acid (43%), palmitic acid (10%), and stearic acid (4%). No adverse effects have been reported by previous trials regarding the external application of this type of SO [9,26,27]. Also, we conducted a pilot study on 10 patients during three months to assess the adverse effects of this type of SO. Based on the pilot study findings, no adverse effects were observed.

In the control group, the same massage procedure was performed but without any topical extract. In both the experimental and control groups, the target site was washed with baby soap and sterile normal saline solution (0.9%) before each massage, and the site was dressed with sterile gauze and fixed with a hypoallergenic adhesive immediately after each massage. In two groups, massage was performed twice a day (every 12 h at 8:00 a.m. and 8:00 p.m.) from the first day of recruitment for seven consecutive days by an expert nurse (the fourth research assistant) in the participating ward.

2.6. Data collection

All patients were examined for phlebitis by the assistant oncologist using the VIFS developed by Jackson. This scale includes observation of catheter for any potential risks during the treatment with PVC and/or signs of phlebitis observed at any stages of phlebitis development and grading. Phlebitis grading is determined based on the VIPS score (0: no signs of phlebitis, 1: possible signs of phlebitis, 2: early signs of phlebitis, 3: medium stage of phlebitis, 4: advanced stage of phlebitis, and 5: thrombophlebitis) [29] (Fig. 1). This scale has been validated by Schultz and Gallant, and is currently one of the main tools for staging of phlebitis [8,30,31]. Following the diagnosis of phlebitis, inclusion criteria checklist was completed through interviews before the random allocation. Then, demographic and clinical characteristics were collected using the patients' clinical records and interviews and by a researcher-made form, including items on age, gender, marital status, educational level, body mass index (BMI), white blood cells (WBC) count, hemoglobin (Hb), and location of phlebitis.

The pain severity at the affected site was rated and recorded as the primary outcome by the VAS, a specified measure for pain assessment including a continuous scale with two end-points of zero and 10 (0: no pain, 1–3: mild pain, 4–7: moderate pain, and 8–10: intense pain) [33]. Patients determined their level of agreement by indicating a position on the gamut. This scale is reliable and valid enough to assess pain in patients with CIP [32,33].

As the secondary outcome, adverse effects of the intervention (i.e., any signs of allergy or sensitivity, bleeding, and infection) were evaluated daily based on the main researcher's observations and the patients' reports. Moreover, probable adverse effects were recorded via phone calls for patients who withdrew or lost the follow-up.

The data were collected at four time points: the first, third, fifth, and seventh days of the intervention. On the first day of intervention, as the baseline, demographic and clinical data and pain severity were documented. On the third, fifth, and seventh days, the pain severity was evaluated and scored in both the experimental and control groups. To conceal the application of SO, we conducted all the evaluations and scorings approximately 6 h after the morning intervention by a blinded nurse (the fifth research assistant) in the participating ward. Prior to all evaluations, the dressing of the affected site was removed and then applied again at the end of the next massage session by the fourth research assistant (who performed the massage).

2.7. Statistical analysis

All the statistical analyses were performed using SPSS version 18. Descriptive statistics were employed to analyze the clinical and demographic information. The Chi-square or Fisher's exact tests, and the independent samples *t*-test were performed to assess the homogeneity of groups for demographic and clinical characteristics of the patients. Due to the non-normal distribution of male and female patients between the experimental and control groups, gender was considered as a covariate in all the analyses. To compare the mean changes of the pain

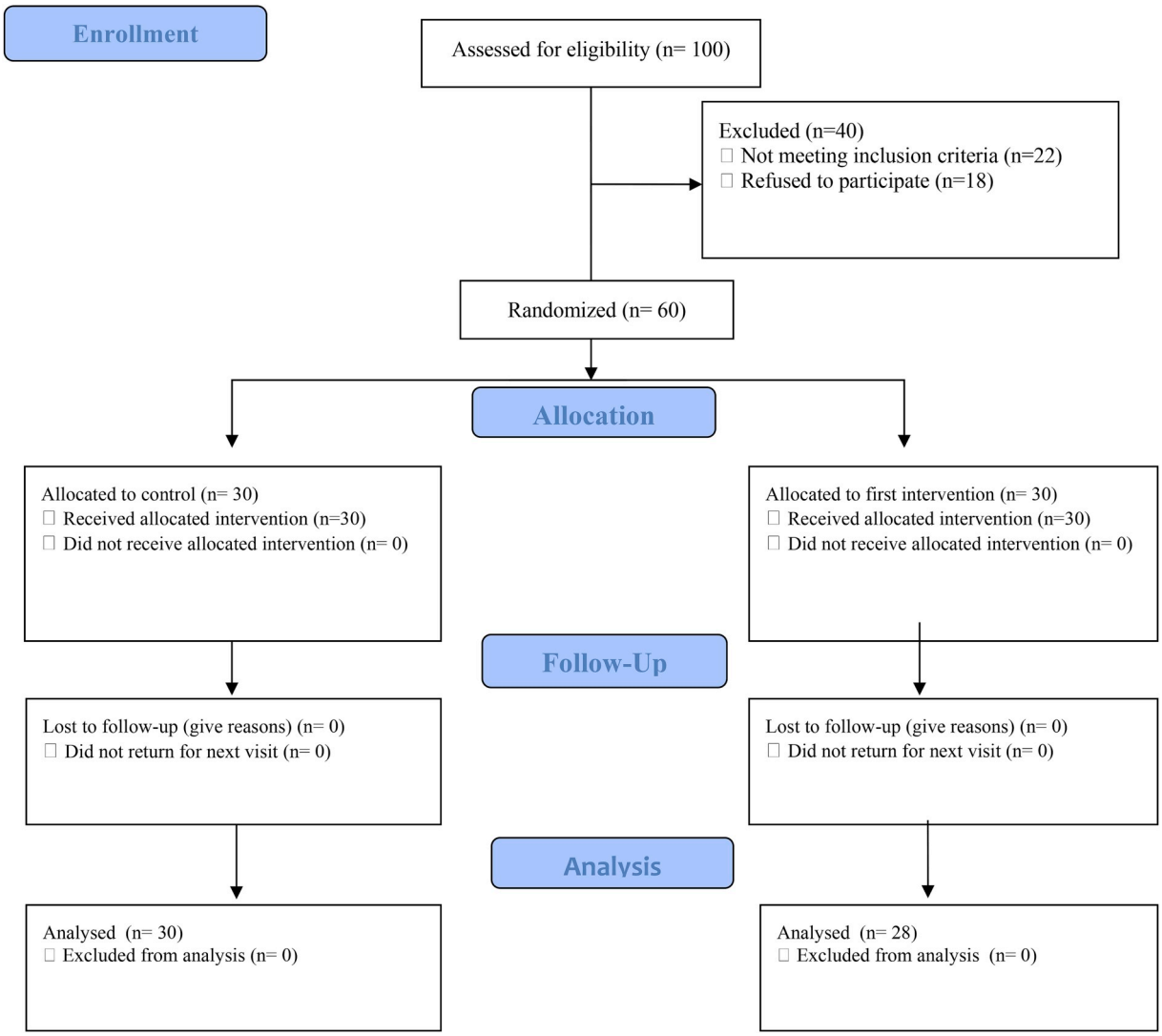

Fig. 2. The CONSORT follow diagram of the patients' recruitment.

severity on the third, fifth, and seventh days of the intervention compared to the baseline between the experimental and control groups, we employed analysis of covariance (ANCOVA). Repeated measures analysis of variance (rANOVA) with Bonferroni correction was applied to determine the effects of the interventions on the pain severity. *P*-value < 0.05 was considered significant in all analyses.

3. Results

3.1. Follow-up

Of the 100 eligible patients, 22 did not meet the inclusion criteria and 18 refused to participate. Of the remaining 60 patients, all adhered to the study protocol and were included in the final analysis (Fig. 2).

3.2. Demographic and clinical characteristics

The differences between the experimental and control groups in terms of demographic and clinical information are shown in Table 1. The number of female patients was higher in the experimental group than the control. No other significant differences were observed in terms of the baseline characteristics, particularly baseline pain severity, between the two groups ($P > 0.05$).

3.3. Primary outcome

The pain severity of both experimental and control groups are presented in Table 2 and Fig. 3. By considering gender as a covariate, rANOVA revealed a significant decrease in the pain severity during the seven days ($F = 720.66$, $P_{time} < 0.001$). Based on the intra-group data using the Bonferroni correction, the mean of changes in pain severity between all two assessment days were significantly different both in the experimental and control groups ($P < 0.001$). However, the decrease in the pain severity was more significant in the experimental group ($F = 21.46$, $P_{group} < 0.001$). Also based on the inter-group data using ANCOVA, the mean changes of the pain severity compared to the baseline were significant on the third (-2.30 ± 0.16 vs. -1.60 ± 0.19, $P = 0.009$), fifth (-4.70 ± 0.16 vs. -2.80 ± 0.25, $P < 0.001$), and seventh (-6.80 ± 0.24 vs. -3.76 ± 0.31, $P < 0.001$) days of the intervention in favor of the experimental group.

3.4. Secondary outcome

At the end of the trial, none of the patients experienced any adverse effects related to the intervention.

Table 1
Demographic and clinical characteristics of the patients with phlebitis in the experimental and control groups.

Variables		Experimental group[a] (n = 30)	Control group[b] (n = 30)	*P*-value
Age (year)	25–40	10 (33.3)	13 (43.3)	0.62[c]
	41–55	15 (50.0)	14 (46.7)	
	56–70	5 (16.7)	3 (10.0)	
Gender	Female	21 (70)	12 (40)	0.02[c]
	Male	9 (30)	18 (60)	
Marital status	Single	2 (6.7)	1 (3.3)	0.83[c]
	Married	26 (86.7)	27 (90.0)	
	widow	2 (6.7)	2 (6.7)	
Educational level	Illiterate	5 (16.7)	10 (33.3)	0.11[c]
	Less than diploma	11 (36.7)	6 (20.0)	
	Diploma	8 (26.7)	12 (40.0)	
	Collegiate	6 (20.0)	2 (6.7)	
BMI (kg/m^2)	BMI ≤ 19	1 (3.3)	3 (10.0)	0.77[c]
	19 < BMI ≤ 25	22 (73.3)	21 (70.0)	
	25 < BMI ≤ 30	6 (20.0)	5 (16.7)	
	BMI > 30	1 (3.3)	1 (3.3)	
Hb	9 ≤ Hb < 12	26 (86.7)	22 (73.3)	0.16[c]
	12 ≤ Hb < 14	3 (10.0)	8 (26.7)	
	Hb ≥ 14	1 (3.3)	0 (0)	
WBC count	WBC ≥ 4000	1 (3.3)	1 (3.3)	0.95[c]
	4000 < WBC ≤ 10000	22 (73.3)	21 (70.0)	
	WBC > 10000	7 (23.3)	8 (26.7)	
Phlebitis sites (vein)	Metacarpal	9 (30.0)	9 (30.0)	1.00[c]
	Cephalic	6 (20.0)	6 (20.0)	
	Basilic	6 (20.0)	6 (20.0)	
	Median cubital	9 (30.0)	9 (30.0)	
Baseline pain severity		8.20 ± 0.99	8.00 ± 1.36	0.51[d]
FOLFOX-4 regimen for the first day in a week	Oxaliplatin (mg/m^2)	79.95 ± 3.33	80.14 ± 4.22	0.842[d]
	Leucovorin (mg/m^2)	198.20 ± 6.97	200.50 ± 6.01	0.177[d]
	5-Fluorouracil bolus (mg/m^2)	403.46 ± 6.61	401.03 ± 6.18	0.147[d]
	5-Fluorouracil infusion (mg/m^2)	599.73 ± 7.52	600.43 ± 12.29	0.791[d]
FOLFOX-4 regimen for the second day in a week	Leucovorin (mg/m^2)	200.20 ± 5.47	201.20 ± 5.22	0.472[d]
	5-Fluorouracil bolus (mg/m^2)	403.96 ± 5.53	401.76 ± 5.39	0.124[d]
	5-Fluorouracil infusion (mg/m^2)	601.06 ± 6.46	601.76 ± 11.58	0.774[d]

BMI: Body mass index, Hb: Hemoglobin, WBC: White blood cells.
All values are expressed as number (percent) or mean ± standard deviation (SD).
[a] Received a 5-min massage with sesame oil on phlebitis site twice a day for seven consecutive days.
[b] Received a 5-min massage solely on phlebitis site twice a day for seven consecutive days.
[c] Chi-square test or Fisher exact test (where appropriate).
[d] Independent samples *t*-test.

Table 2
Comparison of the pain severity between the experimental and control groups on the first, third, fifth, and seventh days of the intervention.

Pain score*	Control group* (n = 30)	Experimental group** (n = 30)	Changes compared with the baseline		
			Control group	Experimental group	P-value†
Baseline (first day)	8.20 ± 0.18	8.00 ± 0.24	–	–	–
Third day	6.60 ± 0.23[a]	5.70 ± 0.30[a]	−1.60 ± 0.19	−2.30 ± 0.16	0.009
Fifth day	5.40 ± 0.30[a,b]	3.30 ± 0.28[a,b]	−2.80 ± 0.25	−4.70 ± 0.16	< 0.001
Seventh day	4.43 ± 0.37[a,b,c]	1.20 ± 0.24[a,b,c]	−3.76 ± 0.31	−6.80 ± 0.24	< 0.001
P-value††		Time			F = 720.66, P < 0.001
		Group			F = 21.46, P < 0.001
		Time*group			F = 61.35, P < 0.001

All values are expressed as mean ± standard error (SE).
*Measured by the visual analog scale that ranked the pain severity from zero to 10.
*Received a 5-min massage with sesame oil on phlebitis site twice a day for seven consecutive days.
**Received a 5-min massage solely on phlebitis site twice a day for seven consecutive days.
†Analysis of covariance (ANCOVA), considering gender as a covariate.
††Repeated-measures analysis of variance (rANOVA), considering gender as a covariate.
[a]Significant compared with the baseline.
[b]Significant compared with the third day.
[c]Significant compared with the fifth day.

4. Discussion

Our findings indicated that the pain severity significantly decreased on the third, fifth, and seventh days of the intervention in patients who received the massage with SO compared with those who received the massage solely. In addition, as the intervention progressed and the time passed, more pain reduction was observed in the experimental group. However, the experimental group included more female patients, and

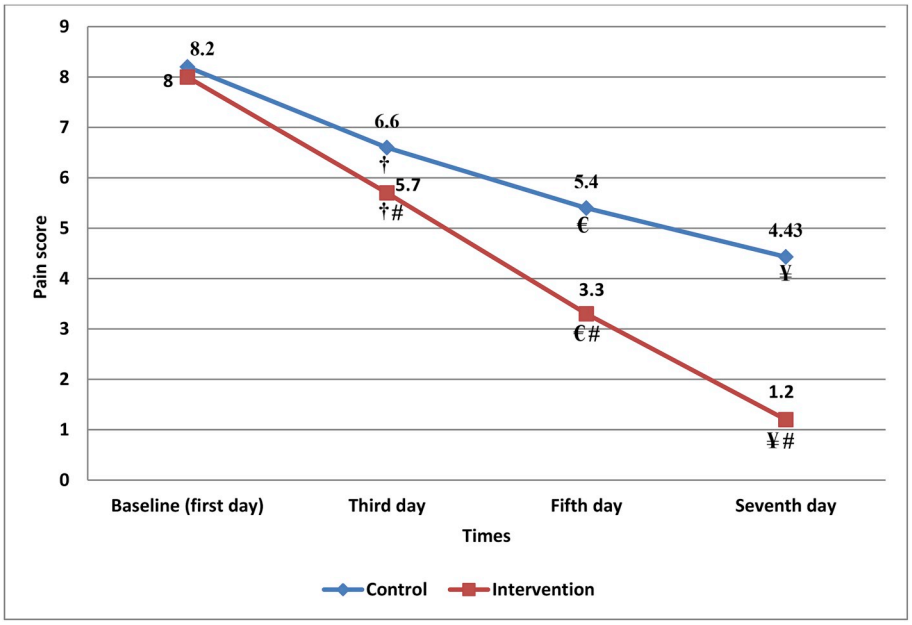

Fig. 3. Comparison of the pain severity between the experimental and control groups on the first, third, fifth, and seventh days of the intervention. [†Significant compared with the first day ($P < 0.001$), €Significant compared with the third and first days ($P < 0.001$), ¥Significant compared with the first, third, and fifth days ($P < 0.001$), #Significant difference between two groups ($P < 0.001$)].

gender was considered as a covariate in all the analyses. It is widely reported that females have greater pain sensitivity and risk for clinical pain compared with males due to some contributing factors (i.e., multiple biological and psychosocial processes). Moreover, responsiveness to pain interventions was greater in females [34]. Thus, it seems that the pain as reported by the patients following the massage with SO might be more than the actual pain in female patients, and it could be assumed that massage with SO may alleviate the pain in patients with CIP.

Based on the available literature, most previous trials have assessed the effects of SO on the management of CIP. In a pilot non-blinded randomized trial on adults with colorectal cancer, Nekouzad et al. indicated that topical application of 10 drops (about 2 mL) of SO (Saman Sesame Oil Co., Iran) on the anterior forearm twice a day for two weeks significantly reduced the incidence and severity of CIP in comparison with the control group [9]. Although the target population and also brand and dosage of SO in this study were similar to the research conducted by Nekuzad et al., some differences should be considered. This study applied either massage or SO plus massage for one week by an expert nurse and the pain severity of CIP as the main outcome was recorded at four certain times. However, in the study by Nekuzad et al., the intervention was conducted during two weeks, SO was applied only by the patients, the incidence and severity of CIP as the main outcomes were rated only before and after the intervention, no massage was given to the phlebitis site, and the control group did not receive any specific interventions.

In another double-blind trial among children with acute lymphoblastic leukemia, Mosayebi et al. found that applying 10 drops (about 5 mL) of pure SO (Barij Essence Pharmaceutical Co., Kashan, Iran) on the anterior forearm twice a day for 30 days significantly diminished the incidence and severity of CIP in comparison with the same drops of placebo (liquid paraffin) [2]. Despite the fact that our findings support the results of the study carried out by Mosayebi et al., the differences in patients' characteristics, brand of SO, duration of the intervention, assessment outcomes, and employment of the placebo should be taken into consideration. Also in the study performed by Mosayebi et al., SO was applied without any massage to the infusion site by a qualified nurse at hospital or one of the family members at home after discharge. However, in current study all massages were applied by an expert nurse in the participating ward.

In addition to CIP, the effect of topical application of SO on amiodarone-induced phlebitis was reported in a recent double-blind clinical trial among the patients hospitalized in a cardiac care unit. Bagheri-Nesami et al. demonstrated that rubbing five drops of pure SO (Barij Essence Pharmaceutical Co., Kashan, Iran) within the 10 cm radius of the amiodarone infusion site four times a day (in 6-h intervals) significantly reduced the incidence, severity, and the onset of amiodarone-induced phlebitis, in comparison with the liquid paraffin [9]. Our findings are in accordance with those obtained by Bagheri-Nesami et al. on the effects of topical SO in the management of phlebitis. However, the difference in patients, type of phlebitis, brand and dosage of SO, employment of the placebo, duration of the intervention, assessment outcomes, and assessment times should be regarded in comparison with the findings of this study.

Some other recent studies have supported the effects of moist exposed burn ointment (MEBO), containing SO plus β-sitosterol, berberine, and other Chinese herbal remedies, in the prevention and treatment of phlebitis. In a recent meta-analysis of randomized controlled trials, it was concluded that MEBO, in comparison with the conventional therapies, significantly reduced the incidence of phlebitis [35]. Junying et al. reported the effectiveness of MEBO for the management of phlebitis caused by extravasation of chemotherapeutic drugs [36]. In another study by Cho et al., it was observed that MEBO had therapeutic effects on the phlebitis of preterm infants caused by total parenteral nutrition fluid extravasation injuries [37]. Even though these investigations evaluated SO in combination with other extracts and on other types of phlebitis, the results are consistent with those of this study on the effects of SO for the management of phlebitis.

In this trial, patients who received massage with SO experienced less pain severity, compared to the control group. Hence, the observed effects in this trial is likely to be related to the topical application of SO rather than massage; however, this effect might have been increased by the massage. Although no mechanism has been identified for the effect of topical SO on phlebitis, the analgesic activities of this oil, which are attributed to its chemical composition, could be effective in reducing the pain severity of phlebitis. SO contains considerable amounts of unsaturated fatty acids (i.e., linoleic acid, oleic acid, palmitic acid, and stearic acid), which can alleviate pain by reducing the prostaglandins and leukotrienes [38,39]. Moreover, SO has lignans (i.e., sesamin, sesamolin, sesaminol, sesamolinol, and pinoresinol) that are responsible for its analgesic and anti-inflammatory activities [39–41].

4.1. Study limitations

Some limitations of this study should be addressed. First, pain relief varies among the individuals due to genetic and demographic differences; this might affect the results. Second, patients and the nurse that performed the intervention could not be blind to the study. Based on the recommendation of the supervising pharmacologist and considering the waxy nature, odor, and color of SO, it was impossible to use a placebo agent in the control group. However, placebo massage was applied to the control group. Third, the evaluation of safety laboratory parameters to consider the adverse effects of SO was not planned due to the short treatment period and the external application of SO. Fourth, a short-time intervention was considered since most samples were outpatients and the intervention could be implemented by an expert nurse in the participating ward under control.

4.2. Clinical implications

In this study, no significant adverse effects were observed for SO; this is in the same line with those of previous trials, showing that topical application of SO was safe and well-tolerated when used for phlebitis prophylaxis [2,9,18]. Thus, it seems that external application of SO is effective, safe, and well-tolerated in phlebitis. Therefore, it can be considered as a method to reduce phlebitis-induced pain in complementary and alternative medicine.

5. Conclusions

Application of massage with SO significantly reduced the pain severity in patients with CIP, considering gender as a covariate. We recommend future studies to assess the safety and feasibility of SO among the patients with different types of phlebitis while comparing the analgesic effects of this oil with other chemical medications or placebo agents in the long-term, considering gender as a main confounding variable. Also, further studies are suggested to detect the biological properties and pharmacological activities of SO as an analgesic agent, especially in phlebitis.

Conflicts of interest

The authors declared no financial or non-financial conflict of interest.

Authors' contribution

MBBS, MM, HB, MSN, and MK: Study conception and design, data collection, data interpretation, and critical revision of the paper; MD: clinical supervision (oncologist), study conception and design, and critical revision of the paper; FM: clinical supervision (pharmacologist), study conception and design, and critical revision of the paper; MN: study conception and design, data analysis and interpretation, manuscript preparation, and critical revision of the paper. All the authors read and approved the final manuscript for submission.

Ethical confirmation

The Ethics Committee and Institutional Review Board of Dezful University of Medical Sciences, Dezful, Iran, approved this study (No. dur-137).

Trial registration

This trial was registered in the Iranian Registry of Clinical Trials (No. IRCT2015041614930N2).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.01.016.

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