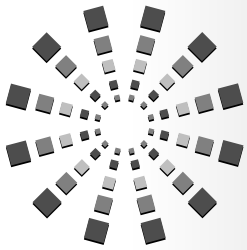

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Cancer-Related Fatigue: A Pilot Study Evaluating the Effect of Frankincense Essential Oil in Patients With Cancer Receiving Chemotherapy

KEYWORDS
Aromatherapy
Cancer
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Essential oils
Fatigue
Frankincense
Supportive therapy
Symptom management

Background: Increasingly, patients with cancer are using essential oils as a complementary therapy to reduce the adverse effects of cancer treatment, such as fatigue. Although essential oils have few adverse effects, little is known about the effectiveness of individual oils for specific symptoms. Frankincense is one such oil that has been identified as a possible supportive therapy for cancer-related fatigue. **Objective:** The aim of this study was to determine if frankincense applied to the soles of the feet before, during, and after chemotherapy affects patients' perceptions of chemotherapy-related fatigue compared with control (carrier oil without frankincense). **Methods:** Randomized clinical trial in which participants were blinded to treatment condition. The main outcome variable was fatigue. **Results:** Seventy patients undergoing chemotherapy for cancer were randomized to apply frankincense or control oil to their feet twice a day 2 days before receiving chemotherapy, while receiving chemotherapy, and 2 days after chemotherapy. No statistically significant changes in fatigue were found over time or between groups. Baseline fatigue was the only predictor of posttreatment fatigue. **Conclusions:** Although no statistically significant changes in fatigue were found over time or between groups, important insights were gained that can inform the design of future research.
Implications for Practice: The use of essential oils as a complementary therapy to reduce adverse effects of cancer treatment is gaining popularity, and nurses may receive questions about the use of essential oils. No evidence to support the use of frankincense in the treatment of fatigue in patients receiving chemotherapy was found in this study.

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Fatigue is the most common complaint of patients undergoing cancer treatment. Upward of 62% of patients will experience fatigue during treatment.[1] The National Comprehensive Cancer Network defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[2(pFT-1)] Cancer-related fatigue profoundly affects quality of life of both patients and their families.[2–4]

The causes of fatigue in individuals with cancer are complex and multifactorial. Chemotherapy and radiation therapy are 2 of the most common types of cancer treatment, and both are associated with an increase in fatigue levels. Other factors that can contribute to fatigue include anemia, medications, psychological distress (eg, anxiety and depression), physical deconditioning, sleep disturbance, pain, nutritional deficiencies, dehydration, infection, comorbid illness, and many other factors.[5] Although many mechanisms have been proposed and are being investigated, the pathophysiology resulting in cancer-related fatigue remains largely unknown.[2]

Treatment of cancer-related fatigue is challenging. Although many treatments have been tested, the only interventions in which effectiveness has been established are physical activity and psychosocial interventions including cognitive behavioral therapies and education.[2,4,5] Complementary therapies such as acupuncture, herbal remedies, massage, essential oils, and the like have been tested, but have not had their effectiveness definitively established.[2,4,6,7] While tightly controlled studies remain to be conducted, very few adverse effects of complementary therapies have been reported, and many patients have anecdotally found complementary therapies to be of benefit.

Studies have shown that the use of essential oils can provide symptom relief in patients with cancer. We were particularly interested in the use of essential oils in aromatherapy as a complementary therapy to reduce adverse effects of cancer treatment intrigued by the reports of symptom relief[8–12] and motivated by clinical experience.[13] Three systematic reviews of more than 40 studies involving more than 3000 patients found that aromatherapies using essential oils relieved various physical and psychological complications.[9,11,12] Lavender, ginger, sweet marjoram, and mandarin essential oils have been reported to reduce pain, anxiety, and nausea, as well as to improve sleep.[10,14,15] Various combinations of peppermint, chamomile, rosemary, coconut, and ginger applied as an aromatherapy massage[16–18] and lavender used in a bath[19] have been reported to have a positive effect on fatigue.

Frankincense essential oil has also been reported to relieve symptoms in patients with cancer.[20] Frankincense has been found to inhibit tumor growth and induce tumor cell apoptosis in a human breast cancer mouse model,[21] cell cultures of human melanoma,[22] and cell cultures of human pancreatic cancer.[23] A *Boswellia*-based cream applied topically has also been found to prevent skin damage from radiotherapy in mammary carcinoma.[24] Frankincense has been used to calm and relax the nervous system, to relieve exhaustion and ease mental fatigue[25]; treat pain[25,26]; and relieve anxiety, depression, and stress.[20,27] One case study used frankincense and lavender essential oils in an inhaler to relax and calm a patient undergoing difficult radiation treatments.[8] Another case study used a 5% dilution of frankincense oil compounded in coconut oil.[13] The oil was applied to the feet of a patient with pancreatic cancer receiving intravenous chemotherapy and resulted in reduced fatigue and improved energy.

Despite the case reports and findings of small studies testing essential oils, the mechanism of absorption and action of essential oils is not understood. One study found that essential oils, including frankincense, promoted permeability and increased skin blood flow when applied to excised mice skin.[28] Others have postulated that the constituents of essential oils act through olfactory pathways connected to the brain, thereby influencing the neuroendocrine system.[8]

The purpose of this study was to determine if frankincense applied to the soles of the feet before, during, and after chemotherapy affects patients' perceptions of cancer-related fatigue compared with the application of a control (the carrier oil alone without frankincense). The hypothesis tested was that after 2 cycles of chemotherapy participants in the intervention group would report significant reductions in fatigue as compared with the control group.

■ Methods

Setting and Sample

This study was approved by the local institutional review board and conducted at a large Midwest community-based cancer center. Patients with cancer 18 years and older receiving intravenous chemotherapy and reporting a fatigue score of 3 or greater (using a 0- to 10-point scale where 0 = none and 10 = unbearable) were recruited for this study. Patients had to have at least 3 chemotherapy cycles remaining in their current course of treatment so that the intervention could be applied over 2 cycles of chemotherapy, and the posttest assessments could be administered just before the next cycle of chemotherapy. Participants were excluded if they had open sores on their feet.

Study Design

This was a randomized controlled trial in which participants were blind to treatment condition. Participants were recruited consecutively as they presented to the cancer center for chemotherapy. Consented participants completed the study assessments in a private office in the chemotherapy clinic immediately following consent. Participants who met the inclusion and exclusion criteria were randomized 1:1 into either the intervention group (frankincense prepared with the carrier oil jojoba) or the control group (jojoba alone). Participants were instructed to apply the oil blend to the soles of their feet morning and evening 2 days before beginning chemotherapy, throughout chemotherapy, and 2 days after the completion of chemotherapy over 2 cycles of chemotherapy.

Application to the soles of the feet was selected as the mode of delivery because they are less prone to sensitivity and irritation and because absorption can be increased when applied to warm, wet, and hydrated skin.[13] The soles of the feet are generally both warm and damp (with sweating). Furthermore, in accordance

with Chinese medicine, the entire body is represented on the feet (eg, reflexology), and so, potentially, the total body experience of cancer-related fatigue could be reduced by applying the frankincense to the soles of the feet. The number of days a participant applied oil and the number of weeks a participant was in the study varied, depending on the chemotherapy regimen they were receiving. Each participant was provided written information about essential oils, how to safely apply the oil, and when to apply the essential oil. After a hands-on demonstration of the process, each participant was asked to give a return demonstration to ensure proper technique.

Assessments were completed at baseline immediately following consent and postintervention after 2 cycles of chemotherapy just before the start of the next chemotherapy cycle. Adherence logs were completed twice daily while participants were applying the intervention.

Intervention

The frankincense (*Boswellia carterii*) essential oil used for the study was purchased from a company that has standards for strict farming, harvesting, distilling, and purity indicators. The National Association for Holistic Aromatherapy[29] recommends a 1% to 5% dilution ratio for essential oils. For this study, five drops (0.25 mL) of frankincense was diluted with 5 mL of jojoba to make a 5% dilution. Jojoba is an odorless, nonallergenic wax commonly used as a carrier for topical applications of essential oils.[20,30,31] The jojoba alone was used as the control oil. The principal investigator prepared the bottles of essential oil blends labeling them "A" and "B"; the coordinator dispensed the bottles according to the randomization scheme. Participants were not informed of the contents of bottles "A" or "B." There was a slight odor to the frankincense preparation if compared directly with the control preparation, but this was not communicated to the participants.

Beginning with the chemotherapy cycle following consent, participants were instructed to apply 2 drops of the oil on the bottom of each foot including the toes, in the morning and the evening (eight drops total per day) 2 days before the start of chemotherapy, throughout chemotherapy, and 2 days after chemotherapy. Participants were advised to wash their hands before applying the essential oil blend, and then 2 drops were placed on the palm of one hand, rubbing it into the bottom of 1 foot (including the toes); the process was repeated with the other foot (again including the toes). After applying the oil, the participant was instructed to put on socks to prevent the oil from rubbing off on the floor/carpet or bed sheets. They were also advised to wash their hands after applying the essential oil blend. If the participant was too fatigued or ill to apply the oil on themselves, a caregiver was to do this for them.

Measures

DEMOGRAPHICS

Demographic data, cancer diagnosis, and treatment information were collected at the beginning of the study. A medical record review was completed by a member of the research team to obtain the participant's hemoglobin from the most recent complete blood count and to confirm the stage of disease. Participants completed the demographic questionnaire.

FATIGUE

Fatigue was assessed using a fatigue visual analog scale (VAS) and the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scale (version 4).[32] Fatigue VAS was measured using an 11-point scale, ranging from 0 (none) to 10 (unbearable). The fatigue score was obtained as part of eligibility and was used to record the morning and evening fatigue ratings in the adherence log. A score ≥4 was considered moderate fatigue and ≥7 severe fatigue.[33] The FACIT-F version 4 scale is self-administered and uses a 5-point Likert rating scale, ranging from 0 (not at all) to 4 (very much). The FACIT-F scale is a 13-item questionnaire that has shown good stability (test-retest $r = 0.90$) and internal consistency (coefficient $\alpha = .95$).[34] Participants completed this scale at baseline and post. The FACIT-F scale ranges from 0 to 52, with lower scores indicating more fatigue. While there are no standardized cut scores for mild, moderate, or severe fatigue, when Cella and colleagues[35] conducted a sensitivity and specificity testing, they determined that patients with cancer who were anemic, with hemoglobin <8 g/dL, had mean FACIT-F scores ≤22 and published this information as a reference point.[35] The fatigue VAS was used as a brief, easily administered measure that was completed at baseline and posttreatment, as well as twice daily during the intervention, whereas the FACIT-F was used to more broadly assess the dimensions of physical, social/family, emotional, and functional fatigue and was administered only at baseline and posttreatment.

PSYCHOLOGICAL DISTRESS (THAT IS, ANXIETY AND DEPRESSION)

Psychological distress was operationalized as anxiety and depression and assessed using the Hospital Anxiety and Depression Scale (HADS).[36] The HADS is a 14-question self-assessment scale of anxiety and depression designed for use in a hospital medical outpatient setting. The patient is asked to reflect on how they felt in the last week and answer 7 specific questions for anxiety and 7 for depression using a severity rating Likert scale ranging from 0 to 3 that indicates the degree of distress. The total HADS score can range from 0 to 42, the anxiety subscale can range from 0 to 21, and the depression subscale can range from 0 to 21. A total HADS score of ≥21 or a subscale score of ≥8 on either the anxiety or depression subscales is indicative of abnormalities warranting additional assessment.[37] Participants completed this scale at baseline and post.

ADHERENCE LOG

Every day, participants applied the intervention they were asked to record whether they received chemotherapy, whether they applied the oil in the morning and evening, and their fatigue rating on the fatigue VAS both in the morning and evening.

Data Analysis

Descriptive statistics were used to summarize participant characteristics. *t* Tests were used for continuous data and χ^2 tests for

categorical data to evaluate demographic, health, and cancer differences between groups. Data analyses were intent-to-treat, using all available pretreatment and posttreatment data from all randomized patients regardless of the extent of treatment participation. To predict posttreatment fatigue as assessed with the FACIT-F, univariate regression analyses were initially run testing each of the assessed predictors of fatigue (ie, treatment group, psychological distress (ie, anxiety and depression), adherence to oil application, type of cancer, stage of disease, cycle of chemotherapy, taxane-containing chemotherapy regimens, hemoglobin, use of steroids, and use of opioids). Then, predictors that achieved significance at unadjusted $P = .05$ in the initial univariate analyses were tested in a simultaneous multiple regression model to identify those predictors that made unique rather than redundant contributions.

Morning and evening fatigue ratings were tracked by participants in logs using a 0- to 10-point fatigue VAS. As the length of chemotherapy administration varied from 1 to 5 days, the mean morning and evening fatigue scores were used to calculate one mean morning and one mean evening fatigue score during chemotherapy to graph changes over time and between the groups. $P < .05$ is considered as statistically significant. All analyses were performed using R 3.6.3 software (The R Foundation, https://www.r-project.org/).

■ Results

Seventy (N = 70) patients with cancer receiving chemotherapy and reporting fatigue levels 3 or greater on a 0- to 10-point VAS were consented into the study and randomized to apply either frankincense and jojoba (active intervention) or jojoba alone (control). All participants were treated as outpatients. Those receiving multiple days of chemotherapy infusions either had an intravenous access device in place for continuous infusions or came into the chemotherapy clinic every day for the duration of their cycle. One participant experienced redness, swelling, and pain of the soles of both feet and both palms of hands during the second application of the oil and was advised by the study team to discontinue participation in the study. Upon unblinding, this participant was found to be using the frankincense. The condition quickly resolved once the oil was discontinued. This was the only adverse event related to the study. See the Figure, the CONSORT (Consolidated Standards of Reporting Trials) chart.

Demographics

Seventy women (n = 54, 77%) and men (n = 16, 23%) agreed to participate in this study; 35 were randomized to apply frankincense, and 35 were randomized to apply the control. The ages of the participants ranged from 28 to 82 years (mean, 59, *sd* = 11.8). The majority of the participants (n = 62, 89%) reported being Caucasian. Almost three-quarters of the sample were married or partnered (n = 49, 70%). The participants were well-educated with over half (n = 37 53%) having educational degrees beyond high school. Only one-third of the participants spent 20 or more hours per week outside the home for work, volunteer activities, or leisure (n = 26, 37%). See Table 1. The 2 groups did not differ statistically in their demographics, except for education which showed marginal significance with 66% (n = 23) of the control group and 40% (n = 14) of treatment group having an advanced education beyond high school ($P = .05$).

Health Status

The presence or absence of eight co-morbidities were queried, ie, cardiac, pulmonary, gastrointestinal, genitourinary, neurologic, endocrine, musculoskeletal, hematologic. Participants reported a mean of 2.4 co-morbidities (*sd* = 1.44). Hemoglobin ranged from 7.9 g/dL to 17.2 g/dL at baseline with a mean hemoglobin of 11.67 g/dL (*sd* = 1.750). More than half of the participants (n = 40, 57%) could be classified as anemic with a hemoglobin <12 g/dL; 15% (n = 11) could be classified as severely anemic with a hemoglobin <10 g/dL. Body mass index (BMI) ranged from 16 to 51 (mean, 30, *sd* = 7.1). Almost three-quarters of the participants could be classified as either overweight (n = 17, 24%) or obese (n = 32, 46%). The 2 groups did not differ in health status. See Table 2.

Cancer History and Treatment

Participants were diagnosed with 11 different cancers, primarily gynecologic (n = 21, 30%) and breast (n = 20, 29%). Two-thirds of the participants (n = 43, 62%) had stage III or IV disease; 17% (n = 12) had recurrent disease. The length of the chemotherapy infusions varied from one to five days, although most participants (84%) had one-day treatments. In addition to chemotherapy, many participants were receiving additional therapeutic treatments including radiation, biologic, and/or hormonal therapies. On average, the participants had already undergone 3 cycles of chemotherapy at enrollment (range, 1-17, *sd* = 2.71). More than half of the participants (n = 39, 56%) were receiving a taxane-containing chemotherapy, 83% (n = 58) were taking steroids, 73% (n = 51) were taking anxiolytics, 49% (n = 34) were taking opioids, and 27% (n = 19) were taking antidepressants. However, the 2 groups did not differ in either their cancer history or treatment. See Table 3.

Compliance With Intervention

Compliance with the intervention was determined by dividing the number of times participants reported applying the oil in their Adherence Log by the number of times they were expected to apply the oil over each chemotherapy cycle (ie, 2 days before the start of chemotherapy, every day while receiving chemotherapy, and 2 days after the completion of chemotherapy). Calculating compliance in this way, an adherence percentage was calculated for each participant over the course of their 2 chemotherapy cycles. Participants applied the oil a mean of 91% of the days they were expected to apply oil. The vast majority, 86% of the participants (n = 54), applied the oil on at least 75% of the days they were expected to apply the oil. The 2 groups did not differ in their compliance with administering the oil. See Table 4.

Fatigue

At baseline, the entire sample of participants had a mean fatigue score of 23.7 (*sd* = 10.00) on the FACIT-F. The study sample

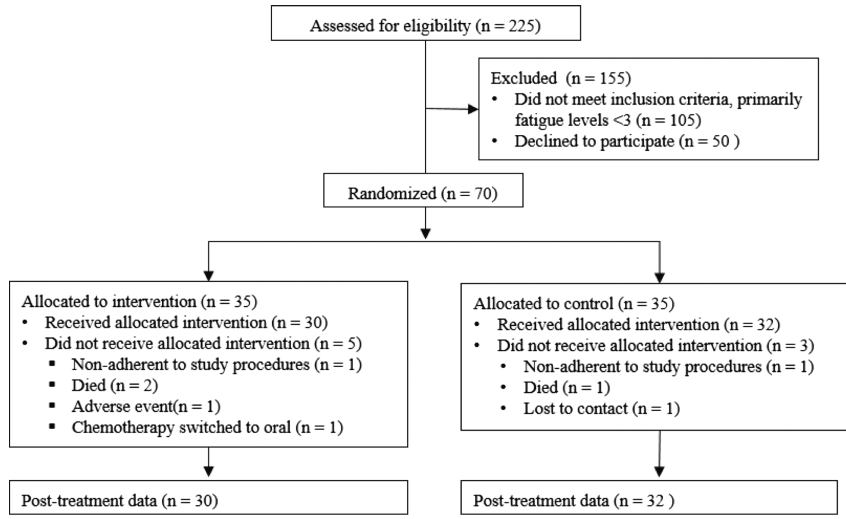

Figure ■ CONSORT (Consolidated Standards of Reporting Trials) chart.

FACIT-F scores were comparable to FACIT-F scores seen in anemic patients with cancer (mean, 23.9, *sd* = 12.6)[35] and significantly more fatigued than either non-anemic patients with cancer (mean, 40.0, *sd* = 9.8)[35] or the general population (mean, 43.6, *sd* = 9.4).[35] Half of the participants (n = 34, 51%) scored ≤22, below the mean for patients with severe anemia. At post-treatment, the entire sample of participants reported less fatigue with a mean FACIT-F score of 27.5 (*sd* = 10.62). At the end

Table 1 • Demographics

	All Participants N = 70	Frankincense n = 35	Control n = 35	*P*[a]
Gender				NS
Female	54 (77%)	25 (71%)	29 (83%)	
Male	16 (23%)	10 (29%)	6 (17%)	
Age, y				NS
Range	28–82	28–82	34–77	
Mean (SD)	59 (11.8)	61 (11.9)	57 (11.5)	
Median	59.5	62	59	
Ethnicity				NS
Caucasian	62 (89%)	32 (91%)	30 (85%)	
African American	3 (4%)	1 (3%)	2 (6%)	
Hispanic	3 (4%)	1 (3%)	2 (6%)	
Other	2 (3%)	1 (3%)	1 (3%)	
Marital status				NS
Married or partnered	49 (70%)	26 (74%)	23 (66%)	
Never married	7 (10%)	4 (12%)	3 (8%)	
Divorced	11 (16%)	5 (14%)	6 (17%)	
Widowed	3 (4%)	0 (0%)	3 (9%)	
Highest educational degree				NS
No educational degree	1 (1%)	1 (3%)	0 (0%)	
High school equivalent	32 (46%)	20 (57%)	12 (34%)	
Associates or specialized training	15 (22%)	6 (17%)	9 (26%)	
Bachelor's degree	12 (17%)	5 (14%)	7 (20%)	
Master's degree	9 (13%)	3 (9%)	6 (17%)	
Doctoral or other professional	1 (1%)	0 (0%)	1 (3%)	
Hours/week spent outside home for work, volunteer activities, or leisure)				NS
>40	15 (21%)	7 (20%)	8 (23%)	
20–40	11 (16%)	8 (23%)	3 (10%)	
10–19	17 (24%)	7 (20%)	10 (29%)	
<10	27 (39%)	13 (37%)	14 (40%)	

Abbreviation: NS, nonsignificant.
[a]*P* value comparing intervention with control.

Table 2 • Health Status

	All Participants N = 70	Frankincense n = 35	Control n = 35	P[a]
No. of 8 comorbidities[b]				NS
Range	0–6	0–6	0–6	
Mean (SD)	2.4 (1.44)	2.8 (1.3)	2.3 (1.5)	
Median	2	3	3	
Hgb (normal for men: 13.5–17.5 g/dL, for women: 12.0–15.5 g/dL), g/dL				NS
Range	7.9–17.20	8.5–17.2	7.9–15.3	
Mean (SD)	11.67 (1.750)	11.78 (1.832)	11.56 (1.683)	
Moderate-severe anemia: Hgb <10 g/dL	11 (15%)	4 (12%)	7 (20%)	
Mild anemia: Hgb 10–12 g/dL	29 (41%)	15 (45%)	13 (37%)	
Normal: Hgb ≥12.01 g/dL	30 (43%)	15 (43%)	15 (43%)	
Anemia: Hgb <12 g/dL	40 (57%)	20 (57%)	20 (57%)	
Normal: Hgb ≥12.01 g/dL	30 (43%)	15 (43%)	15 (43%)	
BMI				NS
Range	16.3–50.7	16.3–39.8	19.8–50.7	
Mean (SD)	29.9 (7.10)	28.6 (6.4)	31.1 (7.6)	
Median	29.4	29.4	30.5	
Normal weight (BMI 18.5–24.9 kg/m^2)	20 (30%)	12 (34%)	8 (24%)	
Overweight (BMI 25–29.9 kg/m^2)	17 (24%)	8 (23%)	9 (26%)	
Obese (BMI ≥30 kg/m^2)	32 (46%)	15 (43%)	17 (50%)	

Abbreviations: BMI, body mass index; Hgb, hemoglobin; NS, nonsignificant.
[a]*P* value comparing intervention with control.
[b]Cardiac, pulmonary, gastrointestinal, genitourinary, neurologic, endocrine, musculoskeletal, hematologic.

of the study, only a third (n = 23, 35%) scored ≤22, below the mean for anemia patients. However, there were no significant changes either over time or between the groups. See Table 5.

Participants recorded their level of fatigue using an 11-point VAS morning and evening. As documented by other investigators,[38–41] participants reported greater fatigue in the evening (mean, 4.3 [SD, 2.47]) as compared with the morning (mean, 3.7 [SD, 2.38]). However, there were no significant changes either over time or between the groups in either morning or evening fatigue. The study hypothesis that participants in the intervention group would report significant reductions in fatigue from baseline to posttesting as compared with the control group was not supported.

Psychological Distress: Anxiety and Depression

Psychological distress was assessed as a possible confounder in the assessment of fatigue. At baseline, half of the entire sample scored in the borderline/abnormal range on the HADS for anxiety (n = 38, 54%) and for depression (n = 36, 51%). Fewer participants scored in the borderline/abnormal range at the completion of study participation (39% for anxiety and 40% for depression), but again, there were no significant changes either over time or between the groups. Neither anxiety nor depression were sensitive measures for the action of frankincense. See Table 6.

Potential Confounders and Predictors of Fatigue

There are many factors that affect fatigue ratings in patients with cancer including the type of cancer; stage of disease; metastasis; type of chemotherapy; number of cycles of chemotherapy; cancer therapies in addition to chemotherapy (eg, radiation); concurrent use of steroids, anxiolytics, opioids, and antidepressants; comorbidities including anemia and psychological distress (ie, anxiety or anxiety); body mass index; and time of day patients are reporting fatigue. However, in our sample, there were no differences in any of these potential confounders between the intervention and control groups. These factors were tested in a regression model to see if any predicted posttreatment fatigue on the FACIT-F. Only baseline fatigue predicted posttreatment fatigue ($\beta = .64$, $P < .0001$).

Limitations of the Study

There were several limitations to this study that could have impacted the ability of this study to detect an effect of the frankincense on fatigue. The length of the chemotherapy regimens varied from 1 to 5 days, and so the dose of the intervention varied as participants were instructed to apply the oil blend each day they were receiving chemotherapy. Even though most participants received chemotherapy 1 day per cycle, the varying doses of the intervention could have influenced the study findings. Fatigue was assessed only 2 days before chemotherapy, during chemotherapy, and 2 days after chemotherapy. While cancer-related fatigue is understood to be at its nadir just before the start of the next chemotherapy cycle, cancer-related fatigue peaks several days after chemotherapy, depending on the type and dose of therapy. We may not have been able to evaluate the potential effect of frankincense when cancer-related fatigue was expected to be at its worst.

We found it surprising that regardless of the intervention, participants reported less fatigue after participation in the study as compared with baseline when we would have expected fatigue

Table 3 • Cancer History

	All Participants N = 70	Frankincense n = 35	Control n = 35	P[a]
Type of cancer				NS
Gynecologic	21 (30%)	11 (31%)	10 (28%)	
Breast	20 (29%)	8 (23%)	12 (34%)	
Head and neck	6 (9%)	4 (11%)	2 (6%)	
Colorectal	5 (7%)	1 (3%)	4 (11%)	
Pancreatic	5 (7%)	3 (9%)	2 (6%)	
Lymphoma	4 (6%)	2 (6%)	2 (6%)	
Hodgkin disease	3 (4%)	3 (9%)	0 (0%)	
Genitourinary	2 (3%)	2 (5%)	0 (0%)	
Lung	2 (3%)	0 (0%)	2 (6%)	
Prostate	1 (1%)	0 (0%)	1 (3%)	
Liver	1 (1%)	1 (3%)	0 (0%)	
Stage				NS
I	8 (11%)	2 (6%)	6 (17%)	
II	16 (23%)	8 (23%)	8 (23%)	
III	21 (30%)	9 (25%)	12 (34%)	
IV	22 (32%)	14 (40%)	8 (23%)	
Lymphoma	3 (4%)	2 (6%)	1 (3%)	
Recurrence (yes)	12 (17%)	7 (20%)	5 (14%)	NS
Treatment in addition to chemotherapy				NS
Radiation	9 (13%)	3 (9%)	6 (17%)	
Biologic	13 (19%)	5 (14%)	8 (23%)	
Other (biologic and hormonal)	1 (13%)	1 (3%)	0 (n/a)	
Cycle of chemotherapy				NS
Range	1–17	1–17	1–12	
Mean (SD)	3.1 (2.71)	2.9 (2.9)	3.3 (2.6)	
Median	2	1	1	
Taxane-containing chemotherapy Regimen (yes)	39 (56%)	17 (49%)	22 (63%)	NS
Steroids (yes)	58 (83%)	29 (83%)	29 (83%)	NS
Anxiolytics (yes)	51 (73%)	26 (74%)	25 (71%)	NS
Opioids (yes)	34 (49%)	20 (57%)	14 (40%)	NS
Antidepressants (yes)	19 (27%)	9 (26%)	10 (29%)	NS

Abbreviation: NS, nonsignificant.
[a]*P* value comparing intervention with control.

to increase as patients underwent additional cycles of chemotherapy. However, looking more closely at the medications patients were receiving, we saw that the majority of participants (n = 58, 83%) were receiving steroids as either part of their chemotherapy premedication or part of their chemotherapy regimen itself. Steroids have been reported to reduce fatigue and improve quality of life[2,3] and the effect of the steroids on reducing fatigue may have obscured our ability to detect any change in fatigue resulting from the intervention. Future studies should consider excluding participants who are taking steroids.

Accurately assessing participant adherence to the study intervention can be challenging. We asked participants to complete daily logs twice a day 2 days before starting chemotherapy, while they were receiving chemotherapy, and 2 days after chemotherapy. Maintaining daily logs twice a day over multiple days can be difficult for some participants, and we had no way to confirm

Table 4 • Oil Application Adherence

Adherence[a]	All Participants n = 63	Frankincense n = 30	Control n = 33	P[b]
Number (%) adherent ≥75%	54 (86%)	25 (86%)	29 (83%)	NS
Adherence				NS
Range in % adherence	0%–100%	50–100	0–100	
Mean % adherence (SD)	91% (14.2)	93 (13.9)	90 (19.7)	

Abbreviation: NS, nonsignificant.
[a]Percent of days applied the oil.
[b]*P* value comparing intervention with control.

Table 5 • Change Over Time in Fatigue

	Baseline	After 2 Cycles of Chemotherapy	Significance of Interaction[a]
Fatigue visual analog scale,[b] mean (SD)			
All participants	4.4 (2.51)	3.9 (3.00)	
Frankincense	4.6 (2.40)	4.2 (3.04)	NS
Control	4.2 (2.62)	3.7 (2.99)	
FACIT-F subscale,[c] mean (SD)			
All participants	23.7 (10.00)	27.5 (10.62)	
Frankincense	22.3 (9.02)	25.6 (10.63)	NS
Control	25.3 (10.90)	29.7 (10.35)	
FACIT-F subscale[c] number/total (%) ≤22 (below mean for anemia patients)			
All participants	34/67 (51%)	23/65 (35%)	
Frankincense	18/35 (51%)	16/35 (46%)	NS
Control	16/32 (50%)	7/30 (23%)	

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; NS, nonsignificant.
[a]*P* value compares intervention with control condition at baseline and after 2 cycles of chemotherapy.
[b]Fatigue visual analog scale range 0-10: 4-7 = moderate fatigue and >7 = severe fatigue.[33]
[c]Fatigue subscale range 0-52: 0 = severe fatigue and 52 = negligible fatigue; scores ≤22 are below the mean for anemic patients.[35]

the fidelity of the data entry and adherence to the study intervention. Participants could have entered multiple days of data at one time informed by previous log entries. Electronic logs with timed reminders might help improve the fidelity of the data collected.

While the control (jojoba) is odorless, the frankincense has a slight odor. The lack of an odor might have indicated to the participants in the control group that they were not receiving the active intervention. The adherence in the control group was less than the intervention group (83% in the control compared with 86% in the frankincense group), but this difference was not statistically significantly different.

Other potential confounders to the assessment of fatigue are sleep disturbance, pain, and exercise behaviors. These factors were not assessed as part of this study but should be considered in future studies. In addition, education as a psychosocial intervention has been shown to be effective in reducing fatigue in patients receiving chemotherapy.[2,3] All participants in this study received education about cancer-related fatigue and ways to reduce fatigue, which could have limited our ability to detect an effect of the frankincense over and above the educational intervention.

■ Discussion

This is the first study we know of that compared the effect of frankincense to control in a sample of fatigued patients with cancer undergoing chemotherapy. However, the lack of control in the type and stage of cancer, type of chemotherapy regimen, and the number of previous chemotherapy cycles, all factors known to influence fatigue, increased the variability in the sample and decreased our ability to appreciate any change in the outcome of interest. Strengths of this study included testing frankincense as a single agent rather than as part of a blend of essential oils and the standardized preparation of the frankincense and control

Table 6 • Change Over Time in Anxiety and Depression

	Baseline	After 2 Cycles of Chemotherapy	Significance of Interaction[a]
HADS[b] anxiety score (range, 0-21)			
All participants	7.0 (4.02)	6.2 (3.72)	
Frankincense	7.1 (3.97)	5.9 (3.61)	NS
Control	6.7 (4.12)	6.6 (3.84)	
HADS[b] anxiety score number/total (%) ≥8 (borderline abnormal or abnormal)			
All participants	38/70 (54%)	24/62 (39%)	
Frankincense	21/35 (60%)	11/30 (37%)	NS
Control	17/35 (49%)	13/32 (41%)	
HADS[b] depression score (range, 0-21)			
All participants	6.3 (3.50)	5.7 (3.03)	
Frankincense	6.5 (3.36)	5.6 (2.96)	NS
Control	6.1 (3.66)	5.9 (3.14)	
HADS[b] depression score number/total (%) ≥8 (borderline abnormal or abnormal)			
All participants	36/70 (51%)	25/62 (40%)	
Frankincense	18/35 (51%)	9/30 (30%)	NS
Control	18/35 (51%)	16/32 (50%)	

Abbreviations: HADS, Hospital Anxiety and Depression Scale; NS, nonsignificant.
[a]*P* value compares intervention with control condition at baseline and after 2 cycles of chemotherapy.
[b]HADS score: 0-7 = normal, 8-10 = borderline abnormal, 11-21 = abnormal.[37]

formulas, allowing participants to be blind to the treatment condition. Whereas other studies have used massage to apply oil,[16–18] this study applied the oil to the soles of the feet controlling for the potential beneficial effects of the massage itself.

Although no statistically significant changes in fatigue were found either over time or between groups, important insights were gained that can inform the design of future research testing essential oils. A 5% dilution of frankincense was applied to the soles of the feet twice a day in this study. While a higher dilution of frankincense is not recommended,[29] testing a more frequent application of oil may be warranted to appreciate an effect of the frankincense on fatigue. Many essential oils are better absorbed if inhaled. Potentially frankincense should be tested as an inhalant. However, identifying an innocuous control with a similar smell could be challenging.

A conceptual framework was not used to guide this study's design; however, as fatigue is such a complex topic with so many risk factors, causes, and manifestations, use of a framework could have helped the study team consider and control for potential confounders as part of the study design. Other insights gleaned that could inform future research include limiting study participation to patients receiving only one chemotherapy regimen known to be causing fatigue, for example, a taxane-containing regimen; consistently administering the frankincense or control throughout the entire chemotherapy cycle; and offering participants different ways to complete the logs (eg, using an app, by email, or over the phone). Limiting enrollment to patients with higher fatigue ratings at baseline, younger patients known to experience more fatigue, sedentary patients not exercising, and/or patients with solid tumors without metastatic disease could also be considered. With only exercise and education proven to be effective in treating cancer-related fatigue, it is possible that the 2 fatigue measures used in this study were not sensitive enough to appreciate change in fatigue from the frankincense over and above the education all participants received and exercise they may have been doing. Future studies should consider other outcome assessments.

Our null findings in light of the number of anecdotal reports of frankincense reducing symptoms[8,13,20,26,27] are puzzling. Additional basic science research is needed to determine the mechanism of absorption and action of essential oils. Are the constituents of essential oils absorbed through the skin and transported through the body in some way? Or do the constituents act through olfactory pathways connected to the brain, thereby influencing the neuroendocrine system,[8] or in other ways? This basic understanding of the mechanism of absorption and action of essential oils is critical to inform conceptual frameworks and the design of future studies.

Implications for Nursing Practice

Nurses often get questions from patients about using aromatherapy to improve their overall health and well-being. Patients report using aromatherapy for symptom management and to increase energy and promote sleep and relaxation. Although this study did not find that frankincense oil applied to the feet twice a day before, during, and after chemotherapy relieved fatigue as compared with control, the findings should be tempered in consideration of the broad study inclusion criteria, variety of chemotherapy regimens administered, and lack of control for interventions known to reduce fatigue (ie, education and exercise). Like other studies,[8] we found the risk of harm from essential oils to be minimal. Only 1 adverse event was recorded for our study (redness, swelling, and pain of the feet and hands) that was managed by stopping the oil application. The National Comprehensive Cancer Network guidelines[2] suggest that if specific causes of fatigue cannot be identified and corrected, then nonpharmacological interventions should be initiated. Nurses can educate patients that although the effectiveness of relieving fatigue with frankincense was not demonstrated in this study, the risk of harm was minimal and manageable.

■ Conclusion

Cancer-related fatigue is prevalent, persistent, and difficult to treat. Although numerous pharmacological and nonpharmacological agents have been tested, only exercise and education have had their efficacy established. Many patients neither want to nor have the energy to exercise. Aromatherapy with essential oils is a common and popular practice for many different conditions, including cancer and cancer-related symptoms. Well-controlled randomized controlled trials need to be done to establish the evidence base for the use of essential oils. Toward this end, this study conducted a randomized controlled study to determine if frankincense applied to the soles of the feet before, during, and after chemotherapy affected patients' perceptions of cancer-related fatigue compared with the application of a control (the carrier oil alone without frankincense). Although no statistically significant change in fatigue was found either over time or between groups, important insights were gained that can inform the design of future research. Additional research is warranted to guide both patient use and practitioner advice in the use of essential oils.

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