

Inhalation aromatherapy in children and adolescents undergoing stem cell infusion: results of a placebo-controlled double-blind trial

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Abstract

Objective: Though often lifesaving, stem cell transplantation (SCT) is a period of great distress for both child and parent.

Methods: We conducted a double-blind, placebo-controlled randomized study evaluating the effect of the respiratory administration of bergamot essential oil on the anxiety, nausea, and pain of 37 pediatric patients with malignant and non-malignant disorders undergoing stem cell infusion and their parents. Patients were assessed at the time of recruitment, prior to infusion, upon infusion completion, and one hour post-infusion using the Spielberger State-Trait Anxiety Inventory (STAI) for parents and the STAIC, Children's Behavioral Style Scale (CBSS), visual analogue scale (VAS) for pain and nausea, and the Emotionality Activity Sociability and Impulsivity instrument (EASI) for children.

Results: Children and adolescents in the treatment group experienced greater anxiety ($p = 0.05$) and nausea ($p = 0.03$) one hour post-infusion. Reported pain in both groups was no longer significant one hour post-infusion. Parental anxiety declined in both groups but did not reach statistical significance. Child's monitoring coping style was significantly predictive of transitory anxiety post-infusion ($p = 0.01$).

Conclusions: Although this trial did not report a benefit of inhalation aromatherapy for reducing anxiety, nausea, or pain when added to standard supportive care, it provides the first experimental rather than descriptive report on testing a single therapeutic essential oil among children and adolescents undergoing stem cell infusion. Future research may consider exploring the cutaneous application of essential oil through massage or other psychoeducational counseling interventions among parents with elevated anxiety and patients with greater information seeking coping styles during SCT.

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Introduction

Stem cell transplantation (SCT) is increasingly common in the treatment of pediatric malignant and non-malignant disorders. Though often life-saving, SCT frequently involves extended hospitalization, numerous acute and long-term side effects, and is generally a time period of great distress for both patient and family [1–3]. Due to its strong and unpleasant sulfurous odor, dimethyl sulfoxide (DMSO) has been associated with the incidence of nausea and vomiting [4] as well as to negatively impact nurse–patient interactions during the infusion of cells among children and adolescents undergoing SCT [5]. Although antiemetics are usually successful in the prevention of emesis,

patients exposed to DMSO may still experience significant levels of nausea. Furthermore, the use of sedative medications, while reducing a child or adolescent's behavioral manifestations of anxiety and perceptions of pain, may not relieve the underlying distress associated with the transplantation experience.

Parental anxiety, a child's coping style and temperament, and SCT associated acute side effects, specifically the high rates of physical discomfort from nausea and vomiting [6] and oral pain from mucositis, may further contribute to a child or adolescent's anxiety during the infusion of stem cells. Successful symptom management during transplantation may help to improve the overall health-related quality of life among

pediatric survivors of SCT [7]. As well, a child's temperament and coping style and disposition to avoid or seek out information may describe how a child will respond to a stressful condition such as SCT [8,9]. In other clinical settings, parental anxiety has been shown to contribute to a child's anxiety during the perioperative period [9], and prior reports have shown substantially elevated parental anxiety among parents of newly diagnosed children with cancer [10]. In addition, anxiety resulting from witnessing one's child undergo SCT may lead to the development of long-term psychological distress among parents [3]. Therefore, interventions to reduce anxiety, nausea, and pain among children and adolescents undergoing SCT for malignant and non-malignant disorders and their parents have become increasingly important.

Complementary and alternative medicine (CAM) therapies are widely popular among children and adolescents with malignant and nonmalignant disorders in the management of various side effects [11,12]. Aromatherapy, defined as the therapeutic use of essential oils, the scented, volatile liquid substances removed from plants using steam or pressure, is an inexpensive and noninvasive CAM practice that dates back centuries to improve wellbeing [13]. The proposed mechanism of action of the respiratory administration of aromatherapy begins with the absorption of volatile odor molecules through the nasal mucosa. Odor molecules are then transformed into a chemical signal, which travels to the olfactory bulb and then amygdala and limbic system, interacting with the neuropsychological framework to produce characteristic effects on target tissues [14].

Though the direct inhalation of essential oils is a popular form of aromatherapy, few clinical trials have investigated its efficacy [15,16]. In an effort to offer patients and their parents an adjunct therapy during stem cell infusion that would reduce anxiety and nausea uncontrolled by conventional medications and limit the stress associated with the transplantation experience, we decided to investigate the efficacy of aromatherapy during stem cell infusion in a randomized trial. The primary aim of this study was to determine the effects of the respiratory administration of bergamot essential oil during the infusion of stem cells on patient and parent anxiety when compared to a scented placebo. Secondary aims were to evaluate its effects on patient reported nausea and pain. Third, we assessed whether parent anxiety and patient's baseline coping style and temperament predicted the occurrence of state anxiety, nausea, and pain during stem cell infusion.

Patients and methods

Study design and patients

A double-blind, placebo-controlled randomized study was performed at the Herbert Irving Child

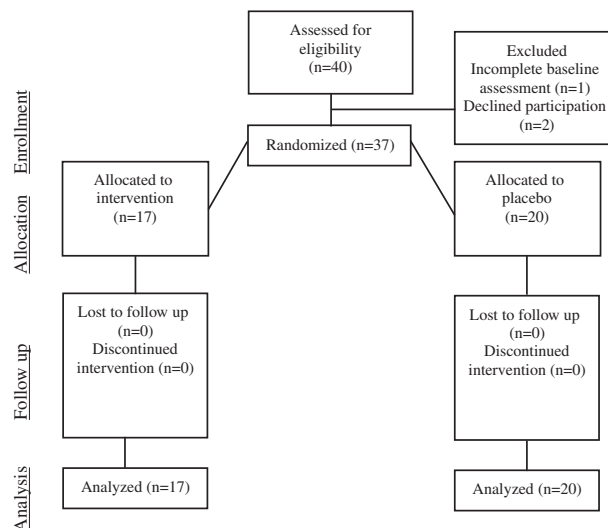


Figure 1. Study design is depicted.

and Adolescent Oncology Center, Columbia University Medical Center (CUMC) among English and Spanish speaking patients with malignant and non-malignant disorders undergoing SCT and between 5 and 21 years of age (Figure 1). Patients who previously received SCT and patients with history of dermatitis or skin reaction related to use of perfumes, aromatherapy, or essential oils were excluded. Informed consent was obtained from all patients, parents, or legal guardians. Assent was obtained from children seven years of age and older. This study was approved by the CUMC Institutional Review Board.

Patients were randomly assigned to receive either inhalation aromatherapy with bergamot essential oil or placebo using an aromatherapy diffuser during transplantation. Randomization was stratified by age (<13 years versus \geq 13 years of age) and transplant type (allogeneic versus autologous) to control for the effect of different conditioning regimens and amount of DMSO in the grafts, and balanced in randomly sized blocks. Patients and study personnel were blinded to treatment allocation. Patients and parents completed assessment measures in the patient's hospital room at four time periods: at recruitment, generally within one-week prior to transplantation (T1), following administration of intravenous medications and prior to stem cell or bone marrow infusion (T2), upon completion of infusion, typically one-hour (T3), and one-hour following completion of the infusion (T4). On the day of transplantation, the aromatherapy diffuser was turned on and filled or refilled with four drops of bergamot essential oil or placebo by the research assistant following the completion of parent and child questionnaires at T2, T3, and T4.

Participation

Patient accrual took place between January 2002 and May 2005. Forty consecutive children scheduled

to undergo SCT for malignant or non-malignant disorders were approached and consented; 37 (93%) subjects completed baseline assessments and were randomized. One subject did not complete baseline assessments and two subjects declined participation on the day of transplantation and were therefore excluded from further analyses.

Aromatherapy application

Bergamot essential oil was chosen based on the aromatherapy literature purporting its use as an anxiolytic and antiemetic in children [17,18]. Bergamot (*Citrus X Bergamia*), a member of the citrus family (*Rutaceae*), was obtained from Elizabeth Van Buren (Santa Cruz, California). The placebo was a non-essential oil-based scented shampoo. Clinical experience and patient reports showed four drops of diffused essential oil per hour would continue to produce fragrance strong enough to be smelled continuously during the time period under investigation. Regardless of age or weight, the same amount of essential oil or placebo was used for all subjects. The Tisserand Aroma-Stream aromatherapy diffuser (Aromatherapy Products Limited, Brighton, England) uses a stream of air driven by a fan to diffuse essential oils and was placed by the child's bedside, in the center of the hospital room, during the period of investigation.

Both the essential oil and placebo were stored in identical amber glass dropper bottles and designated Treatment A/Treatment B. The research assistant was blinded to treatment arm labeling and wore a mask and nose plugs upon entering the patient room to administer questionnaires and fill the diffuser. At consent, both parent and child were informed that both essential oil and placebo contained a scent, though scent type was not disclosed.

Assessment measures

The medical record was abstracted for information on demographics, malignant and non-malignant disorders, disease status, transplant type, prior chemotherapy, conditioning regimen, DMSO amount, and total volume of cells infused. History of prior CAM and aromatherapy use was collected from the subject at T1. A nurse was present throughout the infusion and post-infusion periods to record vital signs, use of additional antiemetic or sedative drugs, and occurrence of emesis or other adverse events. Questionnaires were provided in English or Spanish and read to children under the age of 9 by the research assistant, and older children and adolescents (9–21 years of age) completed the questionnaires independently.

Child Baseline Coping Style was assessed at T1 through the identification of 'monitors,' those who tend to scan for and seek out threat-relevant information when confronted with stressful

situations, and 'blunters,' those who tend to distract themselves and avoid threat-relevant information when confronted with stressful situations, using the Children's Behavioral Style Scale (CBSS) [8]. This scale presents four stressful scenarios to the child and yields a monitoring score and blunting score (range 0–16). When considering monitoring and blunting as conceptually opposite ends of a process continuum, the scale is scored by subtracting the blunting score from the monitoring score; children who score above the median are categorized as 'monitors' and children below as 'blunters.' Alternatively, when monitoring and blunting are considered distinct constructs, scores may be analyzed independently [19].

Child Baseline Temperament was assessed by parent-report at T1 using the 20-item EASI Temperament Survey [20]. The EASI measures four behavioral categories: emotionality, activity, sociability, and impulsivity. Scores range from 5 to 25 for each category, with higher scores indicating higher baseline in each of the respective behavioral categories.

Parent and Child Trait and State Anxiety, our primary outcome, was assessed by self-report using the Spielberger State-Trait Anxiety Inventory (STAI) for parents and the State-Trait Anxiety Inventory for Children (STAIC) for patients [21,22]. STAI(C) contains two separate 20-item subscales that measure state (transitory) and trait (baseline) anxiety. The STAI(C) places distress on a continuum, with a higher score indicating greater anxiety. Comparisons are made to normative data on mean raw scores (\pm SD) separated by gender. Parent and child trait anxiety was assessed at T1 and state anxiety was assessed at all time-points. Baseline state anxiety scores were calculated using the average of T1/T2 STAI(C) state anxiety pre-treatment scores.

Child Nausea was assessed by self-report using a 10 cm Visual Analog Scale (VAS) which asked 'how much do you feel like you have to throw up right now?' *Child Pain* was also assessed with VAS which asked 'how much does your body hurt right now?' The anchors 'not at all' and 'very much' were used at either end of the 10 cm line. Nausea and pain were assessed at all time-points and categorized as percent greater than 0.

Statistical analysis

With a sample size of 40, 20 patients per arm, a two-sided, 0.05-level two-sample *t*-test provided 80% power to detect a relative difference between treatment arms (defined as the treatment difference divided by the standard deviation) of 0.91 on the STAI state and trait subscales. Continuous demographic variables and medical variables were summarized as mean and standard deviation (or median and inter-quantile range if the distribution was skewed) and compared between treatment and control using two-sample *t*-test (or Wilcoxon rank

sum test if distributions were skewed). Categorical demographic variables and medical variables were summarized as count and percentage and compared between treatment and control using chi-squared test (or Fisher's exact test if data were sparse).

Formal analysis of anxiety scores started with a cross-sectional comparison of the two treatment groups using two sample *t*-test for each visit because such analyses are easy to understand. Then, linear mixed effects model was used to assess the treatment effect in patients' and parents' anxiety scores where within-subject correlation was modeled through subject random effects, controlling for baseline covariates such as age, CBSS, EASI, DMSO, and baseline anxiety. Unless the more sophisticated models yielded a significant treatment effect, we chose to present results from a simpler model. The association between STAIC and CBSS and EASI were analyzed using linear mixed effects models, controlling for treatment group. Due to data sparsity, nausea and pain were dichotomized and analyzed using a two-way table and Fisher's exact test. The correlation between patient and parent in the anxiety scores was assessed using a linear model with random subject effects. The statistical analyses were performed in SAS version 9.1 and the figure was generated in R version 2.8.1. A *p*-value of ≤ 0.05 was considered statistically significant.

Results

Sample characteristics

Patients' characteristics together with their disease- and transplant-specific data and prior history of CAM and aromatherapy use are summarized in Table 1. No significant differences were found among patient characteristic variables, including transplant type, use of additional antiemetics/anxiolytics, and adverse events, although the treatment group had significantly greater baseline pain ($p = 0.04$) (Table 2). The majority of the study sample was male (73%) and receiving SCT for a malignancy (84%). Of all patients who had a history of CAM use (59%), 86% had used aromatherapy prior to SCT. Nurse-reported patient adverse events during the infusion and post-infusion periods in the treatment group were nausea ($n = 4$), vomiting ($n = 2$), and hypertension ($n = 5$); use of additional medications among patients in the treatment group with reported adverse events included antiemetics ($n = 1$), anxiolytics ($n = 1$), and hypertension medication ($n = 2$). In the placebo group, nurse-reported patient adverse events during the infusion and post-infusion periods were nausea ($n = 1$), vomiting ($n = 1$), hypertension ($n = 1$), headache ($n = 1$), and chest pain ($n = 1$); use of additional medications among patients in the placebo group with

Table 1. Patient characteristics

Characteristics	Control group (N = 20)	Treatment group (N = 17)	<i>p</i> -Value
Age mean \pm s.d. (median)	12.8 \pm 5.6 (14.5)	11.7 \pm 4.2 (13.1)	0.50
Gender			
Female	6 (30%)	4 (24%)	0.72
Male	14 (70%)	13 (76%)	
Race			0.24
White, not Hispanic	6 (30%)	4 (24%)	
Hispanic other	9 (45%)	5 (29%)	
Black, not Hispanic	2 (10%)	7 (41%)	
Asian	1 (5%)	0 (0%)	
Indian Subcontinent	1 (5%)	0 (0%)	
Other	1 (5%)	1 (6%)	
Ethnicity			0.50
Hispanic	9 (45%)	5 (29%)	
Non-Hispanic	11 (55%)	12 (71%)	
Indications for SCT			1.00
Malignant disorders	17 (85%)	14 (82%)	
Non-malignant disorders	3 (15%)	3 (18%)	
Transplant			0.74
Autologous	7 (35%)	7 (41%)	
Allogeneic	13 (65%)	10 (59%)	
Disease status			0.48
CR	10 (59%)	6 (40%)	
Other	7 (41%)	9 (60%)	
History of CAM use	12 (60%)	10 (59%)	1.00
History of aromatherapy use	11 (55%)	8 (47%)	0.75
Use of additional antiemetic/anxiolytics	9 (50%)	7 (44%)	0.74
Adverse event	5 (29%)	9 (56%)	0.17
DMSO amount (ml) ^a	5.6 (9.6)	5.0 (12.9)	0.78
STAIC trait anxiety score (mean \pm s.d.)	32.9 \pm 7.4	31.9 \pm 7.6	0.71
Coping style (CBSS)			
Median ^a	0 (9)	2 (8)	0.52
Monitoring score	8.8 \pm 4.2	9.5 \pm 3.5	0.61
Blunting score	9.3 \pm 4.3	7.8 \pm 3.5	0.26
Temperament (EASI) (mean \pm s.d.)			
Emotionality	10.6 \pm 4.3	9.3 \pm 3.4	0.32
Activity	13.6 \pm 4.0	15.6 \pm 3.4	0.12
Sociability	18.8 \pm 2.4	18.8 \pm 3.2	0.94
Impulsivity	12.7 \pm 4.0	11.1 \pm 3.6	0.25

CR, current remission; DMSO, dimethyl sulfoxide; STAIC, State-Trait Anxiety Inventory for Children; CBSS, Children's Behavioral Style Scale; EASI, Emotionality, Activity, Sociability, and Impulsivity Instrument of Child Temperament.

^aComputed as median (inter-quantile range), *p*-value from Wilcoxon rank sum test.

reported adverse events included antiemetics ($n = 3$) and pain reliever ($n = 1$).

Child trait anxiety

Mean trait anxiety scores (Table 1) in both groups were lower than those reported in normative data among elementary school students [21]. In normative data mean trait anxiety score for girls was 38.0 (± 6.7) and 36.7 (± 6.3) for boys. Trait anxiety percentile ranks in the treatment group were 43 and 42% and 44 and 43% in the control group respectively for girls and boys.

Child coping style and temperament

As shown in Table 1, there were no significant differences between groups for both child coping style (both mean and median scores) as well as on all subscales of the EASI. Mean CBSS monitoring scores and blunting scores in both groups were lower than those reported in a pilot study of 7- to 12-year-old children, where the CBSS mean of the monitoring subscale was 11.15 (± 2.72) and the CBSS mean of the blunting subscale was 9.56 (± 2.71) [8]. CBSS monitoring score was a significant predictor of child's post-baseline state anxiety at T3 and T4 ($p = 0.01$); CBSS 'monitors,' those above the median combined score, was also predictive of state anxiety ($p = 0.02$) but not of nausea and pain. Parents' proxy-report of child's temperament (EASI) was not correlated with patients' coping style or state anxiety scores. Both groups exhibited the highest baseline temperament

score in *sociability* (a child's general tendency to prefer the presence of others to being alone).

Assessment of parent and child state anxiety

Baseline mean state anxiety for children in both groups was slightly greater than those reported for elementary school students [21] (Table 2). In normative data, mean state anxiety score for girls was 30.7 (± 6.0) and 31.0 (± 5.71) for boys. Baseline state anxiety percentile ranks in both the treatment group and control group were 54 and 54%, respectively for girls and boys. T3 state anxiety percentile ranks in the treatment group were 55 and 56% and 44 and 46% in the control group, respectively for girls and boys. T4 state anxiety percentile ranks in the treatment group were 54 and 54% and 44 and 46% in the control group, respectively for girls and boys. Children in the treatment group tended to experience no change in state anxiety over the course of the study. There was a significant difference in state anxiety between groups with the treatment group experiencing higher state anxiety scores at T3 ($p = 0.01$) and T4 ($p = 0.05$).

Baseline mean state anxiety scores for parents were considerably greater than those reported for working adults [22] (Table 2). In normative data, mean state anxiety score for females was 35.2 (± 10.6) and 35.7 (± 10.4) for males. Baseline state anxiety percentile ranks in the treatment group were 75 and 78% and 85 and 87% in the control group, respectively for female and male working adults (40–49 years of age). T3 state anxiety percentile ranks in the treatment group were 58 and 58% and 67 and 64% in the control group, respectively for female and male working adults (40–49 years of age). T4 state anxiety percentile ranks in the treatment group were 50 and 48% and 49 and 43% in the control group, respectively for female and male working adults (40–49 years of age). Parental anxiety in both groups declined at

Table 2. Anxiety, nausea, and pain at baseline (T1/T2), completion of infusion (T3), and one hour post-infusion (T4)

	Control group	Treatment group	p-value
Child state STAIC score			
T1/T2	32.3 \pm 4.5	32.3 \pm 4.9	0.98
T3	27.8 \pm 4.1	32.5 \pm 5.4	0.01**
T4	28.1 \pm 3.7	32.0 \pm 6.0	0.05*
Parent state STAI score			
T1/T2	46.5 \pm 8.6	42.9 \pm 12.0	0.31
T3	37.8 \pm 10.4	35.8 \pm 13.4	0.63
T4	32.3 \pm 9.3	33.3 \pm 11.2	0.8
Nausea (% of >0)			
T1/T2	45%	71%	0.18
T3	7%	60%	<0.01**
T4	6%	46%	0.03*
Pain (% of >0)			
T1/T2	45%	81%	0.04*
T3	40%	53%	0.72
T4	19%	45%	0.23

Data presented as mean \pm s.d.; STAI, Spielberger State-Trait Anxiety Inventory; STAIC, State-Trait Anxiety Inventory for Children. Higher STAI(C) scores indicate greater anxiety. * ≤ 0.05 , ** ≤ 0.01 .

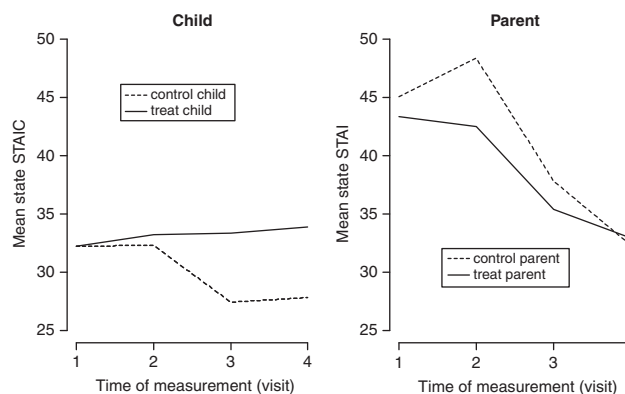


Figure 2. State anxiety levels in patients and parents over time in the treatment group and control group. STAI(C), Spielberger State-Trait Anxiety Inventory (STAI) and the State-Trait Anxiety Inventory for Children (STAIC) respectively. Higher scores represent greater anxiety. Time points: at the time of recruitment (T1), prior to infusion (T2), upon completion of infusion (T3), one hour post-infusion (T4).

T3 and T4, and no significant differences were noted (Table 2). The progression of child and parent state anxiety over the course of the study period is illustrated in Figure 2. No correlation between patients' and parents' state anxiety scores was found ($p = 0.85$). The STAIC and STAI state anxiety reliability for this study was demonstrated by respective Cronbach alphas of 0.60 and 0.74.

Patients' post-baseline state anxiety (T3 and T4) remained greater in the treatment group than in the placebo group when controlling for time-point and baseline state anxiety ($p < 0.001$), and when controlling for baseline pain ($p = 0.003$). No differences in parents' post-baseline state anxiety were detected between groups when controlling for time-point and baseline state anxiety, though there was a decline in the treatment group's parents' state anxiety from T3 to T4 ($p = 0.01$). Patient characteristics and disease and transplant-specific variables were not predictive of patient state anxiety scores.

Assessment of child nausea and pain

Nausea and pain decreased among both groups over the course of the study period (Table 2). Although the treatment group experienced more pain at baseline ($p = 0.04$), pain decreased so as the difference between groups was no longer significant at T3 and T4. Nausea remained greater among the treatment group at T3 ($p < 0.01$) and T4 ($p = 0.03$). Nausea was not a predictor of anxiety among patients ($p = 0.183$). No correlation was found between parent's state anxiety scores and child's nausea ($p = 0.108$) or pain ($p = 0.950$).

Discussion

This is the first study to investigate the use of inhalation aromatherapy among children and adolescents and their parents during SCT. As administered in this study, inhalation aromatherapy with bergamot essential oil did not reduce transitory anxiety and may have contributed to persistent anxiety following the infusion of stem or bone marrow cells among children and adolescents undergoing SCT for malignant and non-malignant disorders. Although no more effective than placebo, parents receiving aromatherapy showed a significant decrease in their transitory anxiety during the period between the completion of their child's infusion and one-hour following infusion. Nausea and pain subsided over the course of the intervention for all children, though nausea remained significantly greater in patients receiving aromatherapy. These findings suggest that the diffusion of bergamot essential oil may not provide suitable anxiolytic and antiemetic effects among children and adolescents undergoing SCT.

Few studies have reported on the pure respiratory administration of essential oils using a placebo-controlled, double-blind study design. In a study of inhalation aromatherapy among 313 adults randomly assigned to receive carrier oil with fractionated oils, carrier oil only, or a blend of essential oils with bergamot concurrently with radiotherapy, anxiety decreased over the course of radiation treatment for all treatment groups, but significant differences in anxiety levels were observed only in the placebo group ($p = 0.04$) [15]. In another double-blind, randomized trial of inhalation aromatherapy among 66 women waiting for surgical abortions assigned to a blend of essential oils with bergamot or a pleasant-smelling hair conditioner (placebo), both groups respectively had significant decreases in anxiety ($p < 0.01$); however, inhalation aromatherapy was no more effective than placebo [23]. This current study suggests exposure to a pleasant odor, whether essential oil or placebo, may have a beneficial effect in reducing preprocedural anxiety. These reports note trends in the reduction of anxiety among all groups which is consistent with our findings among parents and children in the scented placebo group, though not of children in the aromatherapy group.

It is possible that our study results may also be influenced by individual scent preferences and age, as this is the only clinical study to report on the respiratory administration of bergamot among children in this setting. In a recent study of the effect of gender and ethnicity on children's preferences for essential oils, females were significantly more likely to feel 'happy' when smelling sweet orange, a member of the citrus essential oil family, as compared to males ($p = 0.043$) [24]. Differences within gender were also significantly greater among Hispanic females to feel more calm or relaxed when smelling sweet orange ($p = 0.038$). As our sample was primarily male (73%), a greater proportion of our patients may have had a scent preference for a non-citrus based essential oil. The respiratory administration of other essential oils known for their anxiolytic and antiemetic effects, such as lavender [25], peppermint [26], or sweet orange [27] essential oil, or of a familiar, scent that has likely undergone fragrance testing and has pleasant memory associations may have been preferable in this patient population during stem cell infusion.

An appropriate and true comparative dose of treatment to placebo may have been compromised in our study. As demonstrated by Rombola *et al.* [28] and Faturi *et al.* [27] the increased volume of bergamot essential oil has been positively associated with gross behavioral and EEG activity changes in animal models. Varying concentrations of linalool, an oxygenated compound found in the volatile fraction of bergamot essential oil, also demonstrated that inhaled linalool (3% but not at 1% dilutions) was anxiolytic in mice [29]. Additionally, a report by Ollevent *et al.* [30] notes

manufacturer weight differences in the drop size of bergamot essential oil, suggesting that one drop of essential oil may not be equivalent to the dose of one drop of placebo. Because bergamot essential oil causes a dose-related sequence of sedative and stimulatory behavioral effects in animal models [31], it is feasible that the dose administered in this study provoked a more stimulatory rather than calming effect among the children studied, potentially resulting in those children with greater monitoring behavior to have experienced a more enhanced threat to stem cell infusion.

The cutaneous application of essential oil through massage, rather than respiratory administration, may be necessary to achieve a therapeutic effect to reduce anxiety and nausea among children undergoing SCT. Bagetta *et al.* [31] suggests that aromatherapy massage may allow bergamot essential oil to be absorbed into the peripheral tissues, causing a reduction in pain sensitivity. Preliminary reports among patients with dementia indicate positive effects of cutaneous rather than respiratory applications of essential oils for managing behavioral and psychological symptoms [32]. In a large, multicenter, randomized controlled trial among 288 adult cancer patients, clinical anxiety ($p = 0.01$) and self-reported anxiety ($p = 0.04$) were reduced 2-weeks following a four-week course of weekly, one-hour sessions of aromatherapy massage [33]. This study tested an aromatherapy delivery model allowing therapists to prescribe tailored aromatherapy massage treatments, proposing the potential benefits of the cutaneous application of aromatherapy as a therapeutic option for the short-term management of anxiety among cancer patients.

A major strength of our study is the reliability of our results. All baseline characteristics were comparable between groups except for baseline pain, noting a strong randomization. Additionally, the use of controls allowed us to follow trends between the treatment and placebo groups with adequate statistical power and the collection of two baseline measures minimized the variability in emotional functioning one week prior to transplantation. Finally, the use of a longitudinal design under which a subject acts as his or her own control allowed us to make within subject comparisons.

The study was limited by its small sample size consisting of patients with different diagnoses and treatment histories. The degree to which pain and prior high rates of aromatherapy use confounded results warrants further investigation. Although not significant, the treatment group had a higher rate of adverse events, specifically hypertension, possibly contributing to the marked differences in the experience of anxiety and nausea among our sample. Limited baseline data collection also prevented the study investigators to control for other possible predictors, such as prior history of chemotherapy-induced nausea and vomiting or motion sickness

and sensitivity to odors in the analysis. Additionally, we were unable to assess whether the diffusion of placebo decreased anxiety and nausea among our patients due to a scent or treatment effect. As anecdotal reports from both children undergoing SCT and their parents indicated a benefit of the respiratory administration of various essential oils during infusion, future, more definitive trials using a larger sample size, randomization stratified by past aromatherapy experience, and a two-placebo arm study design using a different dose of the same essential oil and a no aromatherapy arm, are warranted. Furthermore, as patients' coping styles and state anxiety scores were not correlated with parents' proxy-report of child's temperament, future trials should consider utilizing both patient and parent reports of coping style and temperament.

Our results demonstrate the need for providing additional supportive care interventions among this patient population to address elevated levels of state anxiety, specifically among children and adolescents who have greater monitoring behavior. As indicated in our study, although not influential in impacting child's anxiety, nausea, or pain during infusion, parental baseline anxiety before infusion of stem cells was considerably high and merits further investigation of interventions helping parents cope with the stress of SCT. Proactive interventions in the weeks prior to infusion among parents and children who are anxious and have a monitoring (information-seeking) disposition are needed. Other CAM interventions or psychoeducational counseling sessions providing information on the infusion process may provide the necessary preparation and should be considered.

Although this double-blind, placebo-controlled trial did not report a benefit in the use of the respiratory administration of aromatherapy when added to standard supportive care, it provides the first experimental rather than descriptive report on testing an aromatherapy delivery using a single therapeutic essential oil among children and adolescents undergoing SCT. Our results specifically report on the use of inhalation aromatherapy using bergamot essential oil and not on the potential benefits of the use of other essential oils in this clinical setting as well as other aromatherapy applications among this population.

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