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Cananga odorata Aromatherapy Reduces Anxiety in Unexperienced Patients Hospitalized for Interventional Neuroradiology Procedures: A Randomized Control Trial

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Abstract

The hospitalization and the unfamiliar experiences of patients in interventional radiology procedures cause a moderate to high levels of anxiety. This study was aimed to evaluate the anxiolytic effect of *Cananga odorata* essential oil (COE) aromatherapy in unexperienced patients hospitalized for interventional neuroradiology (INR) procedures. Forty-four patients admitted for their first INR procedure were randomly divided into COE and placebo control groups. COE or distilled water was dropped onto 2 pieces of mulberry paper and attached to the participant's gown at the shoulder level overnight. The main outcomes were observed from the morning salivary cortisol levels and salivary alpha-amylase activity after intervention. The Thai version of Spielberger State-Trait Anxiety Inventory (STAI) and the vital signs (blood pressure and heart rate) were also assessed before and after COE intervention as the secondary outcome. The demographic and baseline data of both groups did not show any significant difference. After intervention, COE group had a significantly lower salivary alpha-amylase activity than placebo control group. The post-intervention scores of Trait (STAI-T) and State (STAI-S) anxiety were significantly less than those of baseline in both groups. Interestingly, the COE group had a greater percentage reduction on STAI-T after intervention than placebo control group. No significant difference was observed in other outcomes. In addition, the salivary alpha-amylase activity was weak but showed significant correlation with STAI anxiety scores. This study indicates that COE aromatherapy reduces the saliva alpha amylase activity and STAI-T anxiety in unexperienced patients hospitalized for INR procedures.

Keywords

Cananga odorata essential oil, aromatherapy, interventional neuroradiology, anxiety, salivary alpha-amylase

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Introduction

Hospitalization is necessary for the intensive treatment care for the patients preparing for medical procedures. It has been reported that hospitalization causes a moderate to high anxiety levels to these patients.[1,2] High levels of anxiety produce several undesirable outcomes before, during and after the procedure. Increasing heart rate, blood pressure or other sympathetic outflows, and an increasing pain sensation are common possible effects of anxiety. It has been reported that patients with high levels of anxiety need a higher sedation drug dose and are prone to have unwanted movements during sedation.[3,4] In addition, the elevation of blood cortisol level has been reported in anxiety patients and induces the reduction

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of immune systems, causing infection or delays the wound healing.[5,8] Moreover, the effect of cortisol on vessel dysfunction in human atherosclerosis was also reported.[9] The level of anxiety can be assessed using Spielberger State-Trait Anxiety Inventory (STAI) which has been translated into many languages. The assessment of vital signs (blood pressure and heart rate), salivary cortisol levels, and salivary alpha-amylase activities are also known as the physiological responses or the markers of anxiety.[10,12]

Nowadays, the interventional neuroradiology (INR) plays an important role in diagnosis and treatment of neurovascular diseases including cerebral aneurysms, arteriovenous malformation and arteriovenous fistula.[13,15] Since the prevalence of neurological diseases is significantly rised,[16] the diagnosis and treatment procedure using INR is being gained much attention and increased due to its high effectiveness and minimal invasive.[13,15,17]

Several lines of evidence have demonstrated that the moderate to high levels of anxiety were presented in patient undergoing radiological procedures particularly the interventional radiology procedure.[18,20] In addition, the unexperienced patients had greater anxious moments than those with previous experience.[19] Therefore, the unexperienced INR patient who was admitted and prepared for INR procedure had encountered high anxiety that might affect the clinical results. Therefore, findings of strategies to reduce patient's anxiety have been focused on this study.

Numerous studies reported the efficacy of aromatherapy with essential oils on the reduction of anxiety in patients who underwent for medical, radiological and angiographic procedures.[21,26] *Cananga odorata* essential oil (COE) extracted from the flower of *Cananga odorata* (Lam.) Hook. f. & Thomson has been widely used in the aromatherapy manufacturing industry. Such oil was demonstrated to exhibit an anxiolytic effect in animal model and had the sedative effect on healthy volunteers.[27,29] Several clinical studies also revealed the effect of COE on the reduction of anxiety and anxiety related physiological responses.[30,32]

It has been reported that music therapy, providing of multimedia-based information or information provision could decrease anxiety and improve physiological parameters in patients undergoing cerebral angiogram.[33,35] However, the scientific evidence of aromatherapy particularly COE on the reduction of anxiety is still limited. Therefore, this aim of study was to evaluate the effectiveness of COE aromatherapy on the reduction of anxiety in unexperienced patients hospitalized for INR procedure.

Materials and Methods

Study Design

This randomized control trial was performed during 1 November 2019-22 August 2020. The intervention arms were divided into COE group (active comparator group) and placebo control group (sham comparator group). The randomization was performed using block randomization (blocks of 4). The study was conducted in accordance with the International Conference of Harmonization (ICH) for Good Clinical Practice (GCP) and in compliance with the Declaration of Helsinki.

Participant Selection and Sample Size Calculation

All participants were unexperienced patients at the age of 18 years and above who were admitted and prepared for the first INR procedure at the super tertiary care hospital. On the admission day, patients who met the inclusion criteria were asked to participate in the study by INR nurse (co-author) and the well-trained research assistant. Patients who had the following criteria were not recruited into this study; unconscious or unable to communication, anosmia (loss of the sense of smell) or respiratory diseases, allergy to COE, having underlying diseases affected anxiety (depression, heart diseases, endocrine disease or hormone replacement). Participants were provided for the consent prior to their participation in this study and felt free to withdraw from the study anytime. Then, the baseline data including anxiety assessment, general information, and vital signs were recorded.

The sample size was 22 patients per group that reflected the alpha level of 0.05 and the dependent power of 0.80. The calculation formula was a recommended formula for comparison of 2 groups in randomized control trial study.[36] The effect size was based on the study of Pujiarti and colleagues[29] which evaluated the effect of aromatherapy on human physiological responses using saliva-amylase activity. The mean difference of 23.83 in saliva-amylase activity and the pooled standard deviation of 23.27 approximated the effect size at 0.84.

COE and Placebo Control Preparation

The delivery method for COE and placebo control used in this study was a dry evaporation method modified from a previous study.[23] To prepare the aromatherapy tab, the mulberry paper (3.5×3.5 cm) was used as an absorbent material and mounted onto the non-adhesive side of a medical grade adhesive dressing tape (4×4 cm). All tabs were kept in a zip lock bag to prevent dust and to maintain humidity until used.

To perform the COE aromatherapy, the high concentration of COE was purchased from BOTANICESSENCE Essential Oils (Bangkok, Thailand). The certificate of analysis revealed that the constituents of COE were germacrene D (17.27%), benzyl acetate (11.29%), α-farnesene (9.62%), linalool (8.60%), methyl paracresol (8.05%), β-caryophyllene (4.88%), geranyl acetate (4.80%), benzyl benzoate (4.78%), methyl benzoate (4.69%), farnesyl acetate (2.12%) and farnesol (1.17%). On the experiment day, COE (25 µl) was immediately dropped into a piece of mulberry paper. Two pieces of mulberry paper with COE were attached on patient's gown at the shoulder level for 12 h (6 P.M. on the admission day to 6 A.M. on the next day). Patients were asked for their tolerance of COE during the attachment of mulberry paper and informed to freely remove COE if they could not tolerate to its scent during the exposure time.

Fortunately, no participant was withdrawn from this study and neither of them had an adverse event.

To perform the placebo control, 25 µl of the distilled water was dropped onto a mulberry paper and then 2 pieces of mulberry paper with distilled water were placed on patient's gown at the shoulder level for 12 h.

Saliva Collection and Biomarkers Assessment

The morning saliva was collected after removal of COE aromatherapy during 6.00–7.00 A.M. The instruction of saliva collection was adhered to following the guidelines previously reported.[37] After sample collection, saliva was centrifuged at 3000 rpm for 10 min at room temperature. Then, the supernatant was collected and kept in −80 °C freezer until analysis. Anxiety biomarkers including salivary cortisol levels and salivary alpha-amylase activity were assessed by a blinded research assistant.

The salivary cortisol levels was determined by using ELISA kit Abcam ab154996 (Cambridge, United Kingdom) followed by the product instruction with the optical density measurement at 450 nm using microplate reader (iMark™ Microplate Absorbance Reader, Bio-Rad, California, USA). The standard cortisol (0-100 ng/ml) was prepared as a standard calibration curve. Data were expressed as the unit of ng/ml.

The salivary alpha-amylase activity was determined using amylase assay kit Abcam ab102523 (Cambridge, United Kingdom) by colorimetric method following the protocol book of the product. Salivary alpha-amylase activity was measured based on the ability of amylase that could cleave the substrate ethylidene-pNP-G7 to produce nitrophenol, a yellow color substance. The optical density measurement was performed at 405 nm using microplate reader (iMark™ Microplate Absorbance Reader, Bio-Rad, California, USA). The concentrations of nitrophenol (0-20 nmol) were used as to plot a standard calibration curve. Data were expressed as salivary alpha-amylase activity (unit of mU/ml).

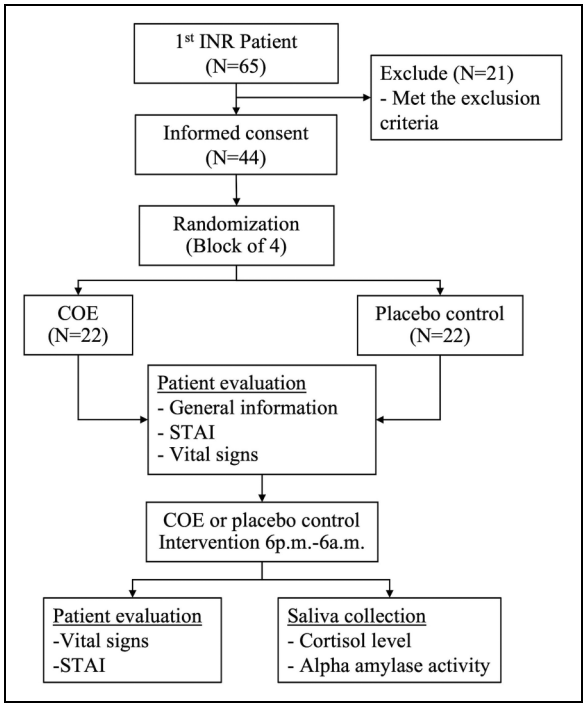

Figure 1. Schematic diagram demonstrated the study procedure.

Anxiety Assessment

The level of anxiety was assessed using Thai version of Spielberger State-Trait Anxiety Inventory or STAI.[38] STAI consists of 2 parts including STAI-State and STAI-Trait. STAI-State was used to measure the state anxiety or the anxiety related to an event of situation while STAI-Trait was used to measure the anxiety level related to personal characteristics. Each part had a score ranging from 20–80 and each question was rated on the 4-point scale (1 = not at all; 2 = sometimes; 3 = frequently; 4 = always). The higher score indicates the higher level of anxiety. After given the inform consent, all participants were assigned to self-rating of the STAI questionnaire under supervision of INR nurses or the well-trained research assistants which presented as baseline data. Each participant took approximately 15–20 min to complete the STAI questionnaire. On the next day after removing of intervention, the STAI questionnaire was assessed again and presented as post-intervention data. The effect of COE aromatherapy on anxiety levels was expressed as a raw score of STAI-State and STAI-Trait at baseline and post-intervention. The percentage reduction of STAI scores was also presented and calculated as the following equation:

$$\%\text{Reduction of anxiety score} = [(\text{Baseline score} - \text{post intervention score})/\text{Baseline score}] * 100$$

The less score and the more percentage reduction of STAI score were associated with less anxiety after COE aromatherapy. In addition, the level of anxiety of all patients were also classified into 3 levels[39] including "no or low anxiety (20-37 points)", "moderate anxiety (38-44 points)" and high anxiety (45-80 points)".

Vital Signs Assessment

The vital signs including blood pressure (systolic and diastolic) and heart rate were performed following by the standard nursing care protocol (6 P.M. and 6 A.M.). The vital signs before and after removal of the COE aromatherapy or control were recorded.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics 19. The normality test was performed using Shapiro-Wilk test. Independent sample t-test was used to analyze the normal distribution data set while Mann–Whitney U test was used to analyze the non-normal distribution data set. In addition, the

paired t-test was also used to analyze the anxiety score at baseline and post-intervention. The comparison of anxiety level was performed using Chi-square test. The correlation was analyzed by using Spearman's correlation. Data was presented as number, percentage, median, mean ± SD and boxplot. p-value<.05 was regarded as significance.

Results

the Demographic Data of Participants

Total 44 patients admitted and prepared for interventional neuroradiology procedure that met the criteria were recruited to the study as shown in Figure 1. They were randomly divided into COE and placebo control group (22 patients/group). The demographic data of patients in both groups is shown in Table 1. There was no significant difference in any parameters between groups. All patients had undergone a diagnostic procedure of 4 main diseases including arteriovenous malformation, dural arteriovenous fistula, carotid cavernous sinus fistula, and aneurysm. The other diseases presented in COE group were moyamoya (2) and venolymphatic malformation at right sternocleidomastoid muscle (1) while the internal carotid artery stenosis (1), moyamoya (1), hypervascular mass (1) and venolymphatic malformation at head and neck (1) were presented in the placebo control group.

Table 1. Demographic Data of Participants in COE and Placebo Control Group.

Demographic data	COE	Placebo control	p-value
Age (Years)	41.68 ± 12.88	44.77 ± 14.00	.45[a]
Education level			
Primary	6	11	.30[b]
Secondary	8	4	
University	6	5	
Others	2	2	
Status			
Single	8	7	.60[b]
Married	12	12	
Divorce	2	0	
Widow	0	3	
Gender			
Male	11 (50%)	11 (50%)	1.00[c]
Female	11 (50%)	11 (50%)	
Diseases diagnosis			
Arteriovenous malformation	8	7	.18[b]
Dural arteriovenous fistula	6	4	
Carotid cavernous sinus fistula	3	4	
Aneurysm	2	3	
Others	3	4	

Data are presented as mean ± SD, number of patients and percentage.
[a]Analyzed using Independent sample t-test.
[b]Analyzed using Chi square test.
[c]Analyzed using Fisher's Exact Test.

the Effect of COE on Anxiety Biomarkers

The anxiety biomarkers including salivary cortisol levels and salivary alpha-amylase activity are shown in Figure 2. The comparison of salivary cortisol levels and salivary alpha-amylase activities were analyzed using Mann–Whitney U test. The result showed that there was no significant difference in salivary cortisol levels between COE (median = 3.88 ng/ml) and placebo control groups (median = 5.43 ng/ml). On the other hand, there were significant differences in the salivary alpha-amylase activity in COE group and placebo control was observed (p-value = .032). The median of salivary alpha-amylase activity in COE group was 48.88 mU/ml (95%CI: 49.80-104.86) while in the placebo control it was 128.43 mU/ml (95%CI 92.07-148.99). It also showed that COE aromatherapy could reduce the salivary alpha-amylase activity in patients preparing for INR procedure to 61.94%. Although, there was no significant differences found in salivary cortisol levels in this study, the COE had a trend to reduce this parameter to 28.54%.

the Effect of COE on STAI-State and STAI-Trait Score

The STAI-State and STAI-Trait score of both groups were presented as raw score at baseline and after intervention (Figure 3) and the percentage reduction of State and Trait score after intervention (Figure 4). Figure 3 demonstrated that the score of STAI-State and STAI-Trait at baseline of COE group were 49.00 ± 8.60 and 45.09 ± 7.56 while placebo control group were 48.05 ± 10.94 and 44.91 ± 8.23, respectively. After intervention, the STAI-State and STAI-Trait score of COE group

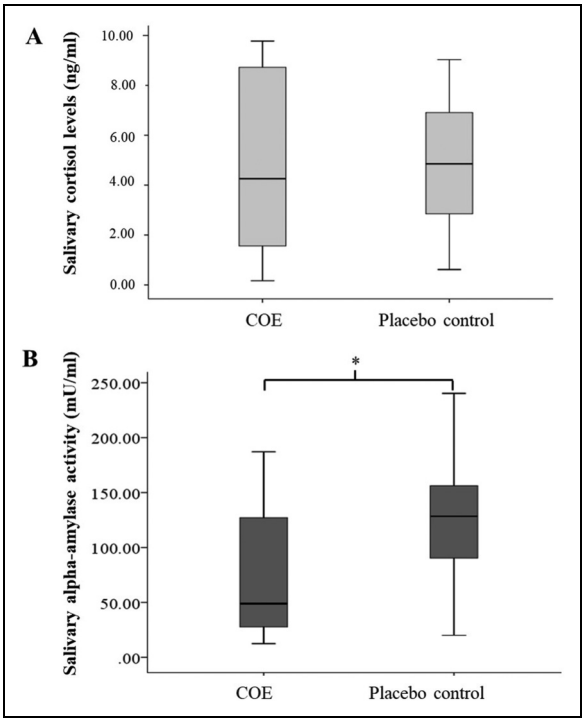

Figure 2. The effect of COE and placebo on the salivary cortisol levels (A) and the salivary alpha-amylase activity (B). N = 22 patients/group.
* Significant difference compared between groups, p-value < .05.

were 39.48 ± 7.73 and 36.64 ± 5.81 while placebo control were 39.91 ± 10.17 and 41.05 ± 9.27, respectively. The comparison of these scores between COE and placebo control group was analyzed using independent samples t-test while the comparison of baseline and post-intervention data was analyzed using paired t-test. The baseline scores of both groups showed no significant difference at the time of admission (p-value>.05). All unexperienced patients admitted and prepared for interventional neuroradiology procedure had the same level of anxiety at the time of admission. After intervention, the STAI-State and STAI-Trait anxiety scores were significantly decreased from baseline data (p-value<.01). However, the significant difference of such scores between COE and placebo control after intervention was not observed (p-value>.05). Since the significant reduction of anxiety score after intervention was found, the percentage reduction of State and Trait anxiety score was also performed. Interestingly, the data in Figure 4 revealed that patients in COE group (15.66 ± 15.89%, median = 17.12%) had a greater percentage reduction of STAI-Trait score than placebo control group (7.31 ± 16.62%, median = 10.53%) with a significance (p-value = .032). No significant difference was observed on the percentage reduction of STAI-State between COE (18.52 ± 11.24%, median = 19.53%) and placebo control group (15.39 ± 12.73%, median = 11.48%).

the Effect of COE on the Level of Anxiety

The levels of anxiety of all patients are shown in Table 2. The result indicated that the number of patients in each classification of anxiety level (low anxiety, moderate anxiety and high anxiety) of STAI-State and STAI-Trait was not significantly different at the baseline (p-value>.05). After intervention, COE aromatherapy was significantly associated with the STAI-Trait level of anxiety (p-value = .049). The number of patients with high anxiety level in COE group was reduced from 12 (54.55%) to 1 (4.55%) while this parameter in placebo control group was decreased from 11 (50.00%) to 7 (31.82%). However, the numbers of patients with moderate anxiety level in COE group (11 patients) were higher than that in placebo control group (6 patients).

the Effect of COE on the Alteration of Vital Signs

At the baseline, Table 3 showed that the systolic blood pressure, diastolic blood pressure and heart rate of patients in both groups were not significantly different (p-value>.05). After intervention with COE or placebo control, all vital signs also showed no significant difference in both groups (p-value>.05).

the Correlation of Anxiety Biomarkers and STAI Score

Results revealed a significant reduction of salivary alpha-amylase activity in the observed COE group. Therefore, the correlation of this parameter and the STAI scores was

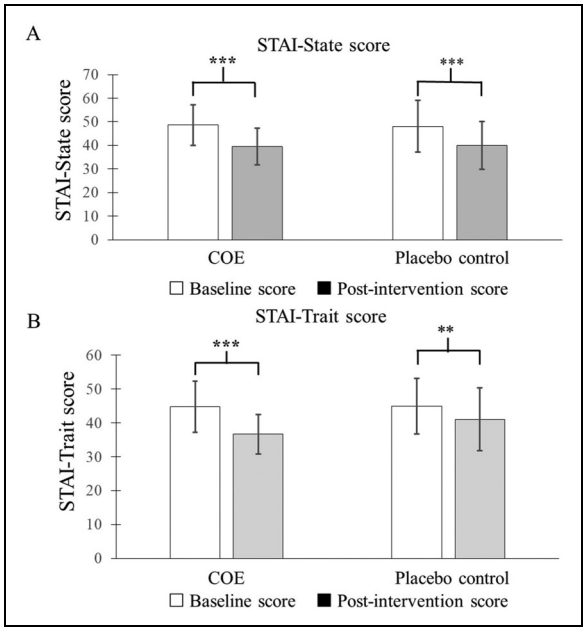

Figure 3. STAI score at baseline and after intervention of COE and Placebo control. (A) STAI-State score and (B) STAI-Trait score. N = 22 patients/group. **,*** Significant difference compared between baseline and post-intervention, p-value < .01 and .001.

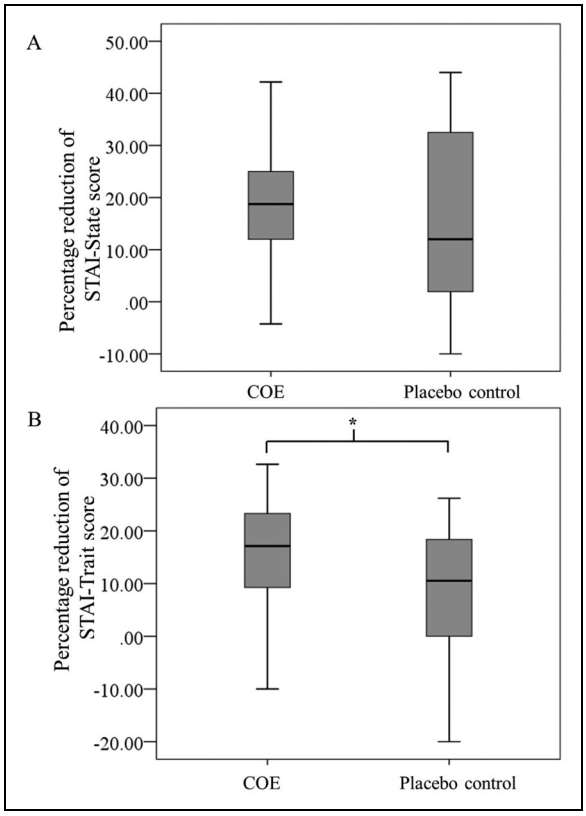

Figure 4. The effect of COE and placebo on the percentage reduction of (A) STAI-State score and (B) STAI-Trait score. N = 22 patients/group. *Significant difference compared between groups, p-value < .05.

further analyzed (Figure 5). It was found that salivary alpha-amylase activity had a negatively weak and significant correlation with percentage reduction of STAI-State and STAI-Trait (p-value = .004, $r_s = -0.437$; p-value = .004, $r_s = -0.450$).

Discussion

The results of this study demonstrated the anxiolytic effect of COE aromatherapy in unexperienced patients hospitalized for INR procedure. Salivary cortisol and salivary alpha-amylase are the key biomarkers for anxiety. AlMaummar and coworkers revealed that the salivary cortisol levels are the markers for a long-term anxiety exposure while amylase is for a short-term anxiety exposure.[40] Since the intervention period of this study was only 12 h, it was less to differentiate efficacy of COE intervention on the salivary cortisol levels. In contrast, salivary alpha-amylase is appropriate for acute condition induced anxiety and commonly used as a biomarker to assess the anxiety.[41,42] This study confirmed that salivary alpha-amylase activity is a strong biomarker for assessment of anxiety which produced an association with STAI score. The reduction of salivary alpha-amylase activity in this report might reduce the bias from subjective scoring of STAI questionnaires and confirm the anxiolytic effects of COE.

The level of anxiety either State or Trait was not different in both groups and the levels of anxiety of these patients were moderate to high anxiety levels which corroborated with the same trend as the previously reported in hospitalized patients.[1,2] A previous study reported that numerous factors are associated with State and Trait anxiety particularly the uncertainty of the future and the ability to response to patient care.[1] Moreover, previous studies have suggested that the communication and giving information are the effective methods to reduce patient's anxious.[34,35,43,44] It is interesting that the State and Trait anxiety score in both groups significantly decreased from baseline. It could be explained that all patients were closed contact with INR nurse or research assistant and might receive information from research team which in turn relieved the factors associated with anxiety as mentioned earlier.

The effectiveness of COE on the reduction of State anxiety in breast cancer patients is quite significant during the

Table 2. The level of anxiety of participants in COE and Placebo control groups at baseline and post-intervention.

STAI	COE N (%)	Placebo control N (%)	p-value
State (Baseline)			
Low anxiety (20-37 points)	3 (13.64)	2 (9.09)	
Moderate anxiety (38-44 points)	5 (22.73)	5 (22.73)	0.889
High anxiety (45-80 points)	14 (63.64)	15 (68.18)	
State (Post-intervention)			
Low anxiety (20-37 points)	9 (40.91)	11 (50.00)	
Moderate anxiety (38-44 points)	7 (31.82)	2 (9.09)	0.167
High anxiety (45-80 points)	6 (27.27)	9 (40.91)	
Trait (Baseline)			
Low anxiety (20-37 points)	4 (18.18)	2 (9.09)	
Moderate anxiety (38-44 points)	6 (27.27)	9 (40.91)	0.519
High anxiety (45-80 points)	12 (54.55)	11 (50.00)	
Trait (Post-intervention)			
Low anxiety (20-37 points)	10 (45.45)	9 (40.91)	
Moderate anxiety (38-44 points)	11 (50.00)	6 (27.27)	0.049
High anxiety (45-80 points)	1 (4.55)	7 (31.82)	

Table 3. the Vital Signs of Participants in COE and Placebo Control Group at Baseline and post-Intervention. Data are Presented as Mean ± SD.

Vital signs	COE	Placebo control	p-value
Systolic BP Baseline (mm Hg)	133.14 ± 19.04	126.45 ± 16.53	.23[a]
Systolic BP Post-intervention (mm Hg)	131.73 ± 14.70	129.00 ± 15.96	.32[b]
Diastolic BP Baseline (mm Hg)	73.57 ± 10.49	72.95 ± 10.83	.85[a]
Diastolic BP Post-intervention (mm Hg)	76.45 ± 10.82	76.23 ± 8.98	.61[a]
Heart rate Baseline (bpm)	78.14 ± 14.67	77.77 ± 13.52	.93[a]
Heart rate Post-intervention (bpm)	75.43 ± 9.33	74.27 ± 11.84	.69[a]

[a]Analyzed using Mann Whitney U test.
[b]Analyzed using Independent sample t-test.

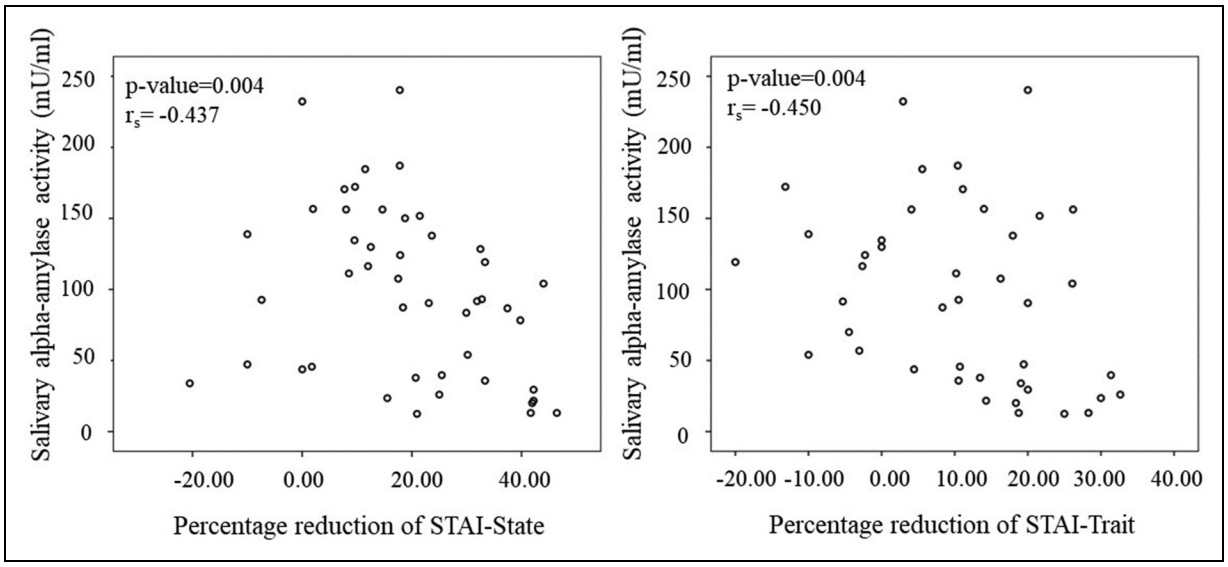

Figure 5. The correlation of salivary alpha-amylase activity and the percentage reduction of STAI-State and STAI-Trait score.

chemotherapy.[32] In this study, the reduction was found in Trait anxiety score and level instead of State anxiety. State anxiety, a psychological and physiological response to the hospitalized situation, can be reduced by the communication between the patients and the research team. Therefore, the intervention of COE did not show any beneficial effect on the State anxiety. On the other hand, Trait anxiety depends on patient's personality. Since the COE possesses sedative and relaxing effect in healthy volunteers,[30,31] these effects might contribute to the important role towards the reduction of Trait anxiety. Moreover, the previous studies have reported the effect of COE on the reduction of heart rate and blood pressure in healthy volunteer after administration of COE for 20–60 min.[30,31,45] However, the changes of these parameters were not observed in this study. It was suggested that the measurement of vital signs after intervention in this study were performed at resting state in all patients. Therefore, it was difficult to observe the difference between COE and placebo control which showed dissimilar result to the previous reports.

The limitation of this study was performing the non-blinded study according to the nature of aroma scent and the placebo that might cause some psychological effects and confound the results. However, all participants were not informed for their group assignments and the intervention was performed in the same step in both COE and placebo control to reduce bias as much as possible. In addition, the investigation and analysis of anxiety biomarkers were performed by a blinded research assistant.

Conclusion

This study indicated that COE aromatherapy could reduce salivary alpha-amylase activity and Trait anxiety in unexperienced patients hospitalized for INR procedure. The reduction of salivary alpha-amylase activity is a potential indicator to confirm the anxiolytic effects of COE aromatherapy. The implementation of COE adjuvant with standard nursing care may exert a beneficial effect for INR patients.

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Author Contribution

Jetsada Sriboonlert: Conceptualization, Methodology, Investigation, Project administrator, data analysis, Manuscript writing; Waranon Munkong: Conceptualization, Patient evaluation; Sunantha Rintawut: Investigation, Patient evaluation; Soodjai Paladkhua: Investigation, Patient evaluation; Ratchalita Suwongsa: Investigation, Patient evaluation; Woranan Kirisattayakul: Conceptualization, Methodology, Data analysis and interpretation, Principle Investigator, Manuscript writing-Editing.

Ethical Approval

This study protocol was approved by Khon Kaen University Ethics Committee for Human Research (HE621144) and registered in the Thai Clinical Trials Registry (TCTR20200513002).

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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