The FAFA Trial: A Phase 2 Randomized Clinical Trial on the Effect of a Fan Blowing Air on the Face to Relieve Dyspnea in Filipino Patients with Terminal Cancer

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Abstract

Introduction Fan therapy has been suggested by some studies as one of the non-pharmacological supportive interventions to alleviate breathlessness for dyspneic patients with terminal cancer. Unfortunately, data among Asians are limited and there are currently no published data showing that this intervention works among Filipinos—thus this study.

Study Design This study was an open-label, randomized, placebo-controlled, crossover Phase 2 trial. The experimental group had a fan blowing air directly to the patient's face for 5 minutes, and the control group had a fan blowing air to the patient's legs. Treatment crossover was done after a washout period of 1 hour. The primary outcome, which is dyspnea, was measured subjectively using the Modified Borg Scale (MBS). Differences in the patient's respiratory rate (RR) and oxygen saturation were also measured.

Results A total of 48 patients were enrolled in this trial. The mean age of the patients enrolled was 51 years, and the most common primary tumor was lung cancer (21%). In the control group, results showed that the mean difference before and after intervention in the MBS was 0.15, and the mean difference in RR was 0.25. On the other hand, the intervention group showed a statistically significant decrease in the patient's dyspnea as evidenced by a mean MBS decrease of 2.79 ($p < 0.0001$), and a mean RR decrease of 1.88 ($p < 0.0001$).

Conclusion The results of this study reveal that fan on face (FAFA) therapy in terminally ill Filipino cancer patients in addition to the prescribed standard of care can significantly alleviate their level of dyspnea. Thus, FAFA therapy should be considered as an adjunct to standard of care for these patients.

Keywords
- fan on face therapy
- dyspnea
- terminally ill
- cancer
- Filipino

Introduction

Dyspnea is a very common symptom in patients with terminally ill cancer. When refractory, it can be an unpleasant sensation of breathlessness caused by a disease that persists despite optimum treatment directed at the underlying pathology.[1] Furthermore, not only does dyspnea increase the feeling of breathing difficulty, but also alters the patients' quality of life and sometimes even leads to psychological changes such as fear, anxiety, and depression.[2-5]

Unfortunately, dyspnea can be very difficult to alleviate and standard pathophysiological treatments can sometimes fail to satisfactorily relieve the patients' suffering. In these situations, it is imperative to implement alternative but effective measures.[6-8] The effectiveness of these approaches are anchored on the multifaceted nature of dyspnea that involves not only sensory perception, but also cognition and emotion.[9,10] This strategic approach should not be treated as an idea or concept worth trying, but should be considered standard of care as

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recommended by several guidelines—one of which states that all clinicians managing patients with chronic dyspnea should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice.[11]

Various pharmacological and nonpharmacological therapies can be aimed at modulating the perception of breathlessness and the person's response to it.[11,12] A variety of evidence-based nonpharmacological treatment options are available.[13-16] One of the strategies endorsed by the American Thoracic Society is the use of a handheld fan.[17] Although the exact mechanisms responsible for the positive effect of a fan on dyspnea remains to be determined, some theories have been proposed and the most famous hypothesis states that stimulation of trigeminal nerve facial receptors "fools" the brain into believing that ventilator flow is higher than it really is, and in the process decreases the feeling of breathlessness or dyspnea. This effect is believed to be mediated by stimulation of cold-sensitive TRPM8—transient receptor potential cation channel subfamily M member 8—channels present on neurons of the trigeminal nerve and vagal afferents.[18-20]

According to a Cochrane systematic review, the effects of fan use in the management of dyspnea in patients with terminal illness are still not conclusive and subject to ongoing debates and studies.[21] This study is designed to fill in the gap of fan therapy in Filipino patients with advanced cancer, as most previous studies were targeted on the Western population.[22-31]

Alleviating dyspnea in terminally ill cancer patients is a major concern, as one of the goals of palliative care is to provide comfort to the patient. Given the low cost, practical convenience, and immediate response of this approach if proven effective with no adverse effects, a clinical trial evaluating the effectiveness of fan therapy to terminally ill Filipino cancer patients will be of great value.

Objective

The objective of this study is to identify the effect of fan therapy on dyspnea in Filipino patients with terminally ill cancer. Specifically, this study aimed to:

1. Identify the clinico-demographic profile of terminally ill Filipino cancer patients presenting with dyspnea who were included in this study.
2. Evaluate the effect of fan therapy on dyspnea in Filipino patients with terminally ill cancer in terms of subjective improvement.
3. Determine the effect of fan therapy on these patients' respiratory rate (RR) and pulse oxygen saturation (SpO_2).

Materials and Methods

Study Design and Setting

This study is an open-label, randomized, placebo-controlled, Phase 2 trial with crossover design. Patients were recruited at the University of the Philippines–Philippine General Hospital (UP-PGH), charity and private wards, and the UP-PGH Cancer Institute from February to July 2019.

Ethical Considerations

This study was approved by the University of the Philippines–Manila Research Ethics Board (UPMREB Code 2019–050–01). Prior to inclusion to the study, the potential participants were oriented regarding the methodology of the study. Patients who agreed to participate gave an informed consent knowing that they could withdraw their participation from the study at any time. Furthermore, the investigators made sure that the conduct of this study did not, in any way, interfere with the provision of the standard of care deemed necessary for the patient.

Population Selection

Inclusion Criteria

Patients were enrolled in the study if they fit the following criteria: (1) patients diagnosed with metastatic or locally advanced cancer; (2) should be at least 18 years old; (3) dyspnea while sitting or lying at rest with a score of at least 3 points on the Modified Borg Scale (MBS, 0 = no breathlessness, 10 = worst possible breathlessness); (4) Eastern Cooperative Oncology Group (ECOG) performance status of 3 to 4; (5) no cognitive impairment; and (6) willingness to join the study. Also, intubated patients were included as long as their RR was higher than the set ventilation backup rate if they were on assist-control mode, and they were able to give their MBS score.

Exclusion Criteria

Patients were excluded if they have any of the following: (1) fever ≥ 38°C in the preceding 24 hours (to control for active acute infection as a possible confounding variable); (2) hemoglobin level ≤80 mg/dL (to control for anemia as a possible confounding variable); (3) diseases or treatments affecting the trigeminal nerve; and (4) unwillingness to take part in the study.

Interventions and Procedures

Participants who met the inclusion and exclusion criteria were divided into experimental and control group by block randomization. Treatment was composed of two phases with a washout period and crossover in between. Fan on face (FAFA) therapy involved directing a fan (ASAHI Fan Model PF-630) to blow air for 5 minutes across the region innervated by the second/third trigeminal nerve branches. The fan was directed toward one side of the face. The rationale for using 5 minutes of directed airflow was based on previous studies that achieved symptom palliation with this duration.[30-32] Like previous studies, the distance, location, side of face, strength, and swing of the fan was determined as per the patient's preference.[30,31] A standing fan placed on the floor was initially turned on at the lowest speed and was gradually adjusted to increase the speed and strength of the fan breeze. In the control arm, airflow was directed unto the legs with the patient's skin exposed for 5 minutes using the same model of the fan as that used in the intervention arm. We adopted the fan-to-legs method as the control treatment based on previous studies[32-34] Treatment crossover was performed after a washout time of 1 hour.[35,36] Methodology and data collection details are summarized in ►**Fig. 1**.

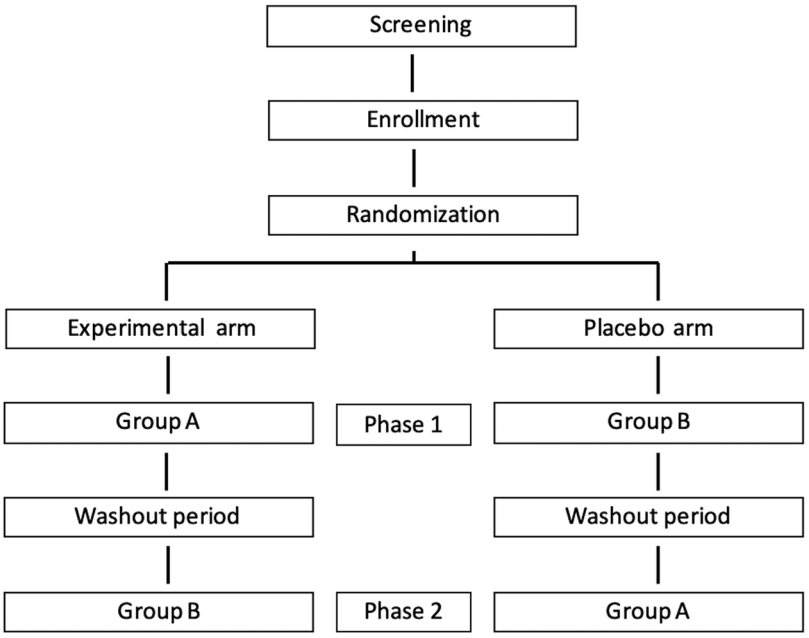

Fig. 1 The FAFA (Fan on Face) trial study design.

Clinical and Demographic Characteristics

Clinical data analyzed included age, gender, cancer type, primary tumor sites, comorbidities (chronic obstructive pulmonary disease, renal failure, pneumonia, pleural effusion), and ECOG performance status.

Outcome Measures

The primary outcome was dyspnea that was measured subjectively using the MBS, a validated 0 to 10 scale to rate the severity of dyspnea. Other objective parameters included RR and SpO_2. These measurements were performed right before (pretest) and after (posttest) treatment in each case.

Statistical Analysis

Descriptive statistics were used for the profiling of the study participants. Comparison of baseline and post-intervention outcome values was conducted using paired *t*-test, while comparison of the change in the outcome values of the placebo and intervention groups was performed using repeated measures ANOVA—analysis of variance. The sphericity assumption was checked for all the repeated measures ANOVA conducted. A 5% level of significance was used in all the hypothesis testing conducted. Both descriptive and inferential statistics were produced using Stata 14 SE.

Sample Size Estimation

Prior data[37] indicate that the mean reduction in dyspnea score using the MBS for dyspnea in the treatment group was 1.53 (standard deviation [SD]: 1.06) and 0.13 (SD: 1.06) for 15 patients each (*t*-test *p*-value 0.0012 and power of 93.70%). Accounting for an α error probability of 0.05 and power of at least 95% under a two-tailed test of hypothesis with a 1:1 allocation per group, a minimum of 32 patients are required.

Results

Clinico-Demographic Profile

The clinico-demographic profile of the 48 patients enrolled in this trial is shown in ►**Table 1**. A total of 24 patients were randomized to initially receive the placebo (fan-on-leg), while the other 24 patients were randomized to initially receive the intervention (FAFA). It can be seen that the mean age of patients, the distribution of gender, primary tumor sites, comorbidities, and performance status did not vary significantly between groups ($p > 0.05$).

Comparison of Baseline Values before and after Washout

Comparison of baseline outcome values before and after washout period were performed within each group using paired *t*-test (►**Table 2**). Results show that the difference between mean baseline values were not statistically significant ($p > 0.05$).

Outcome Measures: Difference between Placebo and Experimental Interventions

Comparison of the change in the outcome values of the placebo and intervention groups were performed (►**Table 3**) using repeated measure ANOVA (the sphericity assumption was not violated in all the comparisons conducted).

The mean change in the MBS score was significantly higher in the intervention group compared with the placebo group (2.79 vs. 0.15; $p < 0.0001$). Similarly, the mean change in the RR was also significantly higher in the intervention group compared with the placebo group (1.88 vs. 0.25; $p < 0.0001$). Lastly, the mean change in the SpO_2 score was significantly higher in the intervention group compared with the placebo group (0.67 vs. 0.10; $p < 0.0001$).

Table 1 Clinico-demographic profile of the patients

Characteristics	Group A (n = 24)		Group B (n = 24)		p-Value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Gender					0.247
Female	11	45.83	15	62.50	
Male	13	54.17	9	37.50	
Primary tumor sites[a]					0.709
Lung	3	12.50	7	29.17	
Bladder	2	8.33	0	0.00	
Lymphoma	1	4.17	1	4.17	
Renal	1	4.17	0	0.00	
Germ cell tumor: mediastinal	1	4.17	2	8.33	
Breast	3	12.50	5	20.83	
Cervical	0	0.00	1	4.17	
Gallbladder	0	0.00	1	4.17	
Osteosarcoma: leg	3	12.50	1	4.17	
Colorectal	2	8.33	2	8.33	
Prostate	0	0.00	1	4.17	
Head and neck tumors	2	8.33	1	4.17	
Esophageal	1	4.17	1	4.17	
Ovarian	2	8.33	1	4.17	
Pancreatic	1	4.17	0	0.00	
Melanoma	2	8.33	0	0.00	
Comorbidities					0.787
COPD	2	8.33	1	4.17	
Renal failure	1	4.17	0	0.00	
Pneumonia	17	70.83	16	66.67	
Pleural effusion	4	16.67	6	25.00	
Pregnancy	0	0.00	1	4.17	
Performance status					0.773
ECOG PS 3	13	54.17	12	50.00	
ECOG PS 4	11	45.83	12	50.00	
	Mean	**SD**	**Mean**	**SD**	
Age	49.79	16.34	52.21	20.00	0.6488

Abbreviations: COPD; Chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
[a]All patients were noted to have lung metastases.

Discussion

A great majority of patients with locally advanced or metastatic cancer experience dyspnea, especially during the terminal phase or when nearing the end of life. Dyspnea in these patients does not only cause physical and psychological distress to the patient, but also to the families and friends.[6,7,38-40] Thus, relieving dyspnea should be one of the clinicians' goal as supportive and palliative care is provided.

The concept of "Total Dyspnea" states that physical, social, psychological, and spiritual factors are shown to influence our patients' experience of dyspnea. This makes us conclude that there are numerous interventions that could be done to alleviate this distressing symptom.[41] These interventions should not only be confined to relieving the structural or physiologic pathology causing the symptom, but also address the subjective experience of dyspnea. This is especially true among the terminally ill from whom invasive and aggressive interventions are, in many instances, opted out.

Although a few studies have shown that FAFA therapy is effective in decreasing dyspnea, the mechanism responsible is still poorly understood. Various theories have been proposed and the most famous hypothesis states that

Table 2 Comparison of baseline values before and after washout period

Group/Outcome	Phase 1 (before washout)			Phase 2 (after washout)			*p*-Value
	n	Mean	SD	*n*	Mean	SD	
Group A							
Modified Borg Scale	24	7.46	0.51	24	7.42	0.50	0.3277
Respiratory rate	24	27.13	1.03	24	27.17	1.24	0.7140
Oxygen saturation	24	96.88	0.80	24	96.75	0.74	0.4170
Group B							
Modified Borg Scale	24	6.83	1.31	24	6.88	1.48	0.5748
Respiratory rate	24	25.08	1.84	24	24.79	2.08	0.1661
Oxygen saturation	24	96.25	1.39	24	96.83	1.17	0.5162

Abbreviation: SD, standard deviation.

Table 3 Comparison of change in outcome values of the placebo and intervention groups

Outcome	Placebo group			Intervention group			*p*-Value
	n	Mean	SD	*n*	Mean	SD	
Modified Borg Scale	48	0.15	0.36	48	2.79	0.92	<0.0001
Respiratory rate	48	0.25	0.44	48	1.88	0.94	<0.0001
Oxygen saturation	48	0.10	0.31	48	0.67	0.75	<0.0001

Abbreviation: SD, standard deviation.

stimulation of the trigeminal nerve facial receptors "fools" the brain into believing that ventilator flow is higher than it really is, and in the process decreases the feeling of breathlessness. This effect is believed to be mediated by stimulation of cold-sensitive TRPM8 channels present on neurons of the trigeminal nerve and vagal afferents.[18-20] This theory is supported by a recent neuroimaging study that showed facial airflow may modify sensory perception of breathlessness in the central nervous system.[42]

The most recent study that explored the benefits of a handheld fan on chronically dyspneic patients showed that 72% of the patients perceived some benefit.[25] Of the 133 patients included in this study, 21 of them had malignant conditions.

Our study focuses on the effect of FAFA therapy specifically for terminally ill Filipino cancer patients with locally advanced and metastatic cancer. The results showed a statistically significant difference between the improvement in the patients' MBS, RR, and SpO_2 between the placebo and experimental group as shown in ►**Table 3** ($p < 0.0001$). The MBS decreased by a mean score of 3 (SD: 0.92) showing similar rates of improvement in a Chinese trial.[37] Furthermore, the minimum clinically important difference in the MBS has been considered as 1 unit,[38] which was clearly achieved in this study.

However, unlike the Chinese trial, this study also showed improvements in RR with a mean decrease of 2 breaths per minute (SD: 0.94) in the experimental arm compared with placebo ($p < 0.0001$). Although the study results show a numerically significant improvement in SpO_2 (mean increase of 0.67%, SD: 0.75, $p < 0.0001$), the authors are cautiously hesitant to conclude that it has any value in terms of clinical significance.

Dyspnea often induces physical and psychological distress thereby promoting anxiety and depression. Also, one of the challenging aspects of dyspneic patients is that most of them present with intermittent dyspnea. This concept increases the importance of FAFA therapy, as its immediate availability could result in the rapid improvement of dyspnea with no known adverse effects.[41]

Limitations

The small sample size and the single-institutional setting remain the major limitations of this study. Possible ascertainment bias is not totally excluded due to the lack of blinding.

Conclusion

This is the first study to provide additional evidence to support the use of FAFA therapy (blowing air from an electric fan directly on the face) specifically for Filipino patients with terminal cancer in addition to the prescribed standard of care. It was shown to significantly alleviate their level of dyspnea as evidenced by a subjective decrease in their MBS score and slight objective decrease in their RR. Thus, FAFA therapy should be considered as an adjunct to standard of care for these patients.

Recommendations

Results of this study can provide future researchers with the first evidence that shows the effectiveness of FAFA therapy in alleviating dyspnea in Filipino patients with terminal cancer. In line with this, a similar but larger-scale and multi-institutional study may be done to increase the generalizability of the findings.

A study on the factors affecting the effectiveness of FAFA therapy in these subset of patients may be explored—factors that encompass but are not limited to optimal duration and method of delivering the intervention (e.g., stand fan vs. handheld fan), and patient factors that are most likely to benefit from FAFA therapy.

FAFA therapy as a safe and accessible adjunct to standard of care should be included in the provision of supportive and palliative care for these patients.

Conflict of Interest

None declared.

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