Effect of Heated Humidified High Flow Nasal Cannula (HFNC) Oxygen Therapy in Dyspnea Patients with Advanced Cancer, a Randomized Controlled Clinical Trial.

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Research Article

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Abstract

Purpose

Heated humidified high flow nasal cannula(HFNC) oxygen therapy is one of the most important oxygen therapy methods, which are commonly applied to relieve dyspnea in advanced cancer patients. Our study aims to observe the efficacy and safety of HFNC oxygen therapy on dyspnea patients with advanced cancer and explore the clinical application.

Methods

60 subjects with advanced cancer requiring oxygen therapy from a Grade 3, Class A hospital in China were recruited and randomized (1:1) to traditional nasal catheter oxygen therapy or HFNC. Primary outcomes were dyspnea, oral dryness and sleep condition, which were recorded after 72-hour treatment. Secondary outcomes were heart rate (HR), respiration rate (RR), S_pO_2, P_aO_2 and P_aCO_2, which were recorded after 2, 6, 24 and 72 hours-treatment.

Results

72 hours after treatment, there were significant improvement in all primary outcomes (P<0.001). PaO_2 and RR were statistically changed 2 hours after HFNC treatment (P<0.001). $PaCO_2$ and HR were statistically changed 24 hours after HFNC treatment (P<0.001).

Conclusion

HFNC oxygen therapy has good effect, high safety and is easy to be accepted by dyspnea patients with advanced cancer. It can be used as the first choice of oxygen therapy for these patients and has broad clinical prospects.

This work was retrospectively registered in the Chinese Clinical Trials Registry (ChiCTR2100049582) on August 4, 2021.

Introduction

Cancer ranks as a leading cause of death in the world[1]. There are many clinical complications in patients with advanced cancer, in which dyspnea is one of the most common symptoms[2]. Dyspnea is a debilitating symptom among advanced cancer patients [3], which can cause physical and psychological distress, severely affect patients' quality of life(QOL)[4–6]. The high prevalence of dyspnea ranges from 21–70% of patients[7]. Unlike cancer-related pain, the standardized treatment of dyspnea has not been well promoted and popularized. Thus, in order to effectively alleviate the dyspnea of patients with advanced cancer, palliative care is needed[8], which is mainly to relieve symptoms, relieve pain, and improve the quality of life. Moreover, with the increase in the demand for improved quality of life and the failure of conventional treatment, such as radiotherapy and chemotherapy, some patients prefer palliative treatment[9].

A review reported that the interventions of cancer-related dyspnea includes opioids, oxygen, psychotropic drugs and nebulized furosemide[10]. Oxygen therapy, non-invasive ventilation and invasive mechanical ventilation are typically the main respiratory support strategies[11] to relieve dyspnea. Among them, Oxygen therapy is widely used because of its convenient use, simple operation and low cost. Oxygen therapy can be divided into low flow and high flow oxygen therapy. The concentration of oxygen inhaled by conventional nasal catheter oxygen inhalation is unstable and cannot be accurately regulated[12]. Moreover, Some patients who use traditional oxygen therapy cannot effectively improve dyspnea, and still face pain and discomfort caused by dyspnea. Recently, High-flow nasal cannula(HFNC), also known as nasal high flow (NHF) oxygen therapy, is a new type of respiratory support technology which can provide accurate oxygen concentration (21-100%) through air/oxygen blender[13], which is a promising novel oxygen delivery device, whose specific mechanisms offer some beneficial effects over conventional low flow oxygen inhalation systems[14]. After heating and humidification, the highest gas temperature can reach 37°C and the humidity can reach 100%. The gas flow rate provided is higher than the patient's suction peak flow rate[15, 16]. HFNC can provide PEEP that may help to improve oxygenation and counteract the effects of intrinsic PEEP on work of breathing, which has been confirmed that can be used in the patients with acute hypoxic respiratory failure [17, 18], patients after surgery[19, 20], patients with respiratory failure without endotracheal intubation [21], and immunosuppressive patients[14], patients with obstructive sleep apnea[22], etc. However, few studies have assessed the effect of HFNC on advanced cancer patients with dyspnea[8].

Thus, the aim of this study was to explore the physiologic effects of HFNC on advanced cancer patients with dyspnea, which can only accept palliative treatment. The changes of S_pO_2, P_aO_2, P_aCO_2, respiratory rate(RR) and heart rate (RR) were observed before and after 2h, 6h, 24h and 72h treatment. The primary outcomes including dyspnea, dryness of mouth, sleep quality were observed before and after 72h-treatment.

Methods

Study design

A randomized, controlled trial was performed in the department of oncology and in the first hospital of Zibo City in China. The trial was approved by the first hospital of Zibo City in China Ethics Committee (No.2019016) and registered in the Chinese Clinical Trials Registry (ChiCTR2100049582). All patients signed informed consent form prospectively.

Patients

Sixty patients with advanced cancer who can only receive palliative treatment from March 2019 to March 2020 in the first hospital of Zibo City in China were consecutively enrolled as the study participants by the research personnel. Inclusion criteria: (I) age between 18 and 80 years; (II) with advanced solid cancer; (III) meeting grade 4 of the mMRC; (IV) the curative treatment was not effective and palliative care was accepted; (V) respiratory rate >30 times/min; (VI) oxygen index < 1:250; and (Ⅶ) signed informed consent form. Exclusion criteria: (I) intolerant, irritable and uncooperative; (II) invasive assisted ventilation was needed for exacerbation of the disease; (III) duration of hospital stay < 3d. All enrolled subjects received training on oxygen therapy in order to gain the trust and cooperation of subjects and their caregivers. The trial was terminated when the patient experienced one of the following conditions (I) did not tolerate oxygen therapy; (II) abandoned treatment for various reasons; and (III) died. All the patients who met the criteria were randomly divided into the intervention group (HFNC oxygen therapy,30) and the control group (conventional nasal catheter oxygen inhalation therapy group,30). Randomization was conducted using random number generated by SPSS version 22.0 random number generator.

Study outcomes

The primary outcomes were dyspnea, oral dryness and sleep quality measured before and after 72 hours. The secondary outcomes were HR, RR, SpO2, PaO2 and PaCO2. Baseline characteristics were collected. Subjects' comfort, including (1) Dyspnea was assessed by Visual analog scale (VAS) dyspnea score. VAS[23] is a horizontal line, 100 mm in length, and anchored by word descriptors at each end, which uses “no shortness of breath at all” and “maximum shortness of breath”. The patients were asked to mark on the line the point that they feel represents their current state. The distance (mm) between the beginning of the horizontal line and this mark represents the degree of dyspnea perception; (2) the degree of oral dryness was evaluated from 0 to 10 points. The higher the value, the drier the oral cavity is; (3) the sleep quality was assessed by the Sleep State Self-Rating Scale (SRSS), which was designed to assess the sleep quality of hospitalized subjects. There are 10 items in total. Each item has a 5-point scale (1–5). The higher the total score, the worse the sleep. This scale has a minimum score of 10 (basically no sleep problems) and a maximum score of 50 (most severe). The changes of respiratory rate (HR), heart rate (RR) and blood oxygen saturation (SpO2) at each time point were monitored by cardiogram monitors. PaO2 and PaCO2 were recorded by blood gas analyzer.

Study procedures

All subjects received palliative treatments. Palliative treatments include (I) Anti-infective treatment; (II) Antiasthmatic drug treatment; (III) Antitussive and expectorant treatment; (IV) Correcting water electrolyte and acid-base imbalance; (V) Nutritional support treatment; (VI) Pain control. The intervention group was additionally treated with HFNC oxygen therapy, using the nasal high-flow heating and humidification oxygen therapy instrument (model: HUMIDIUM-BM, HiFent, Respircare). The appropriate size of nasal cannula was selected for every patient and the temperature of humidification gas was set at 31-37. The inhaled oxygen concentration (FiO2) was adjusted according to the patient's SpO2, ranging from 21–100%. According to patient's degree of dyspnea and tolerance, the flow rate was set between 30-50L/min. In control group, oxygen was inhaled by conventional nasal catheter for more than 24 hours. The oxygen flow was set at 2-8L /min.

Statistical Analysis

SPSS version 22.0(SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. The mean ± standard deviation was used for normally distributed data and the median (interquartile range) [M (P25, P75)] was used when the measurement data were non-normally distributed. Counting data was expressed by a numerical value and the chi-square test was used for comparison between different

groups. The independent sample t test was used to compare the normal measurements between two groups and the Mann-Whitney U test was used to compare the non-normal measurements. Matched samples t- test was performed on data measured at multiple time points. $P < 0.05$ was statistically significant.

Results

Patients

A total of 60 subjects were eligible for inclusion and underwent randomization in the study from March 2019 to March 2020, with 30 in control group(conventional nasal catheter oxygen therapy) and 30 in intervention group(HFNC oxygen therapy). The participant flow diagram (Figure 1) shows that all the subjects completed the whole treatment. Post-hoc manifests 1-βcan reach 0.86 (effect size = 0, α = 0.05).

Baseline characteristics

Table 1 shows the baseline characteristics of all subjects. A total of 60 subjects were enrolled in this study. Before treatment, there were no significant differences between two groups ($P > 0.05$).

Table 1
Baseline patient characteristics before treatment

Baseline patient characteristics	control group	intervention group	*t/Z/χ2*	*P*
age	58.5±10.84	59.2±8.93	-0.273	0.786
gender			0.067	0.795
male	16(53.33)	17(56.67)		
female	14(46.67)	13(43.33)		
heart rate (beats per minute	107.07±10.28	107.8±9.14	-0.292	0.771
respiratory rate (breaths per minute)	30.03±2.94	30.17±3.31	-0.165	0.870
SpO_2	89.30±2.94	88.87±2.97	0.568	0.572
PaO_2	60.26±6.5	60.76±5.5	-0.322	0.749
$PaCO_2$	48.28±5.13	47.08±5.32	0.893	0.375
dryness of mouth score	6.50±1.50	6.07±1.55	1.099	0.276
VAS score	8.57±1.10	8.23±1.36	1.044	0.301
SRSS score	36.97±2.04	36.27±2.00	1.342	0.185

Primary outcome

The dyspnea in intervention group was improved after 72-hour treatment ($P<0.001$), while the dyspnea in control group was not ($P =0.415$). The degree of dryness of mouth after 72-hour treatment was mildly increased without statistical significance in the intervention group ($P =0.056$), while significantly increased the control group ($P < 0.001$). The sleep quality in intervention group was better than before($P < 0.001$), while there is no improvement in control group. The detailed data were shown in table 2.

Table 2 VAS score, Degree of dryness of mouth score and SRSS score before and after 3 day-treatment.

group	VAS score			Degree of dryness of mouth score			SRSS score		
	before	after 3days	*P*	before	after 3days	*P*	before	after 3days	*P*
Control group	8.57±1.10	8.77±1.38	0.415	6.50±1.50	8.13±1.20	<0.001	36.97±2.04	37.47±2.39	0.247
Intervention group	8.23±1.36	6.80±0.48	<0.001	6.07±1.55	6.47±1.55	0.056	36.27±2.00	30.27±2.05	<0.001
P	0.301	<0.001		0.276	<0.001		0.192	<0.001	
P<0.05 indicates that there is a statistical difference in this index between groups and within each group.									

Secondary outcomes

The Blood gas analysis(PaO2, PaCO2) and SpO2 at different time points

PaO2 increased to varying degrees over time within the two groups. The difference of PaO2 between two groups was statistically significant after 2, 6, 24 and 72 hours (P< 0.001). PaCO2 in intervention group was lower than that before treatment after 24 and 72 hour-treatment(P< 0.001) and was lower than that in control group after 24 and 72 hour-treatment (P< 0.001). SpO2 began to increase after 2-hour treatment in intervention group and after 6-hour treatment in control group (P< 0.001). SpO2 in intervention group increased statistically at each time point compared with the previous time point.

Table 3 SpO2, PaO2, PaCO2 at different time points

Index	before	After 2h	After 6h	After 24h	After 72h	*F*	*P*
Control group							
SpO_2	$89.30±2.94^{cde}$	$89.90±2.82^{cde}$	$90.97±2.19^{abde}$	$91.30±2.22^{abce}$	$92.20±2.38^{abcd}$	26.058	<0.001
PaO_2	$60.26±6.50^{de}$	$61.13±5.52^{de}$	$60.67±5.03^{de}$	$77.46±5.49^{abce}$	$78.85±7.08^{abcd}$	253.200	<0.001
$PaCO_2$	48.28±5.13	48.39±5.47	48.09±5.19	48.02±3.76	47.91±3.62	0.211	0.767
Experimental group							
SpO_2	$88.87±2.97^{bcde}$	$92.23±2.32^{acde*}$	$93.93±1.80^{abde*}$	$94.90±2.26^{abce*}$	$95.87±1.80^{abcd*}$	112.104	<0.001
PaO_2	$60.76±5.5^{bcde}$	$71.01±6.42^{acde*}$	$81.47±4.9^{abde*}$	$83.03±6.41^{abce*}$	$84.62±6.33^{abcd*}$	634.688	<0.001
$PaCO_2$	$47.08±5.32^{de}$	$46.89±5.52^{de}$	$46.52±5.23^{de}$	$43.86±4.64^{abce*}$	$43.04±4.53^{abcd*}$	41.709	<0.001
* indicates a statistically significant difference compared with control group; a indicates that the comparison within the group was statistically significant compared with that before treatment(*P* <0.001); b, c, d, e indicates that the comparison within the group was statistically significant compared with 2h, 6h, 24h, 72h after treatment(*P*<0.001) respectively. *P* <0.05 indicates that the comparison at different time points within each group was statistically different.							

Physiological indicators(RR, HR) at different time points

RR and HR began to decrease after 2-hour treatment in intervention group, while after 6-hour treatment in control group (P< 0.001). After 6, 24 and 72 hours, there were statistically significant differences in RR between two groups(P< 0.001). After 24 and 72 hours, there were statistically significant differences in HR between two groups (P< 0.001).

Table 4 RR, HR at different time points

Index	before	After 2h	After 6h	After 24h	After 72h	*F*	*P*
Control group							
HR	107.07±10.28^{cde}	107.77±9.75^{cde}	102.27±9.58^{abde}	101.50±9.97^{abde}	99.17±9.10^{abcd}	143.943	<0.001
RR	30.03±2.94^{cde}	29.93±2.46^{cde}	29.37±2.65^{abde}	28.40±2.76^{abce}	27.70±3.25^{abcd}	25.134	<0.001
Experimental group							
HR	107.8±9.14^{bcde}	104.8±5.96^{acde}	101.7±8.25^{abde}	96.87±6.44^{abce*}	93.53±6.96^{abcd*}	161.908	<0.001
RR	30.17±3.31^{bcde}	28.9±1.73^{acde}	27.6±3.48^{abde*}	26.57±3.86^{abce*}	25.33±3.26^{abcd*}	48.133	<0.001

* indicates a statistically significant difference compared with control group; a indicates that the comparison within the group was statistically significant compared with that before treatment(p <0.001); b, c, d, e indicates that the comparison within the group was statistically significant compared with 2h, 6h, 24h, 72h after treatment(P<0.001) respectively. P <0.05 indicates that the comparison at different time points in the group was statistically different.

Discussion

To the best of our knowledge, this is the first randomized controlled trial using HFNC in advanced cancer patients. In this study, we found that HFNC can enhance patients comfort, which is reflected in the decrease of VAS score, dryness of mouth score, and SRSS score. The beneficial effects of HFNC in several objective parameters, such as RR, HR, SpO2, PaO2, PaCO2 were also showed.

There are several explanations for the decrement of dyspnea. First, HFNC can increase expiratory resistance of the nose because of the different sizes of the cannula and the jet-flow effect against exhaled gas [24]. The expiratory pressure will further prolong the duration of exhalation, so decreasing respiratory rate. The slower and deeper breathing can decrease the work of breathing[25–27] and increase tidal volume[24], which can decrease the proportion of dead-space volume and then improve breathing efficiency[24]. Thus, patients can breathe more comfortably with less dyspnea. Compared with HFNC, the conventional nasal catheter oxygen inhalation provides oxygen at flow rates <15 L/min[28–30]. It lacks the ability to wash out the nasopharyngeal dead space and decrease work of breathing. Secondly, HFNC can decrease anatomical dead space in the upper airway, which is attributed to the high flow effect[14, 24]. Nasopharyngeal dead space washout can reduce rebreathing of expired air and CO_2, create a fresh oxygen reservoir within the upper airways[31, 32], thus improving breathing efficiency and reducing tachypnea[24, 33–35]. Thirdly, the high flow of delivered gas which exceed the patient's demand can help overcome resistance during inspiratory period[36]. Meanwhile, the inspiratory air-flow dynamics is improved with HFNC, as evidenced by the fact that the pressure remained above atmosphere for most of the inspiratory phase[24]. This increase would help subjects overcome resistance and raise the driving pressure for inspiration, thus decrease work of breathing and dyspnea. Fourthly, HFNC therapy delivers a low level of positive airway pressure in expiratory phase[37–39] which contributes to lung compliance increment, alveoli recruitment and end-expiratory lung volume increment[40]. Thus, the oxygenation was improved and the dyspnea was lessened. Lack of humidification, secretions in the airways, such as sputum, become thicker and harder to expel, making it more likely that subjects with advanced cancer will experience dyspnea[41]. As is shown before, HFNC plays a vital role in heating inspired gas close to body temperature level (37°C) and humidifying the respiratory system to saturation, especially in high flow rates, where conventional nasal catheter oxygen inhalation fail [36, 42]. The mucociliary function and secretion elimination is facilitated[43]. Furthermore, the required metabolic cost of warming and humidifying of inspired gas is reduced, especially in subjects whose RR are increased with advanced cancer[33]. Thus, another reasonable explanation is the fully and effectively humidification of HFNC, which can help subjects clear airway more easily and relieve dyspnea. Owing to mechanism mentioned above, the effect of HFNC on dyspnea was better than that of conventional nasal catheter oxygen inhalation among patients with advanced cancer.

Dryness of the mouth can be caused by breathing dry or insufficiently humidified oxygen[44], which may frequently result in discomfort. AARC Clinical Practice Guideline suggested that the humidification provided by the nasal mucosa becomes insufficient when administered at flow rates exceeding 4 L/min[11]. The consist of an active heated humidifier of HFNC system allows patients to be administered fully humidified high-flow oxygen[13], thus the HFNC system reduced discomfort related to symptoms of mouth dryness in patients with advanced cancer. Several investigators have reported that improving the humidification of the inspired gas ameliorates patient comfort, which is congruent with our study[44].

Owing to the less dyspnea and dryness of the mouth by using HFNC, sleep quality was significantly improved in the experimental group after intranasal high-flow oxygen inhalation, while there was no significant change in control group.

HR and RR were chosen to reflect the degree of improvement of vital signs before and after treatment. As is mentioned above, the high flow of HFNC can flush out the dead space in upper airway ,improve gas exchange and lung volume, enhance the breath efficiency and increase tidal volume, thus HNFC exert various effects in the respiratory system, especially lower respiratory rate and effort[18]. We speculate that owing to the comfort of patients which is attributed to lower work of breath and less dyspnea, HFNC can reduce anxiety in patients. Thus, with less anxiety, the patients are calmer, which helps the heart rate decreased.

Based on the observation about persistent improvement of SpO2 measured by pulse oximetry, we can conclude that HFNC is associated with greater overall oxygenation[17]. First, the conventional nasal catheter oxygen inhalation provides oxygen at flow rates that are lower than patients' inspiratory demands. As a result, the room air is entrained and administered oxygen is diluted[36]. The final concentration of oxygen truly delivered to the patient can be lower than the set FIO2 initially(FIO2SET). On the contrary, the HFNC which has the ability of generating high flow rates up to 60L/min that can even exceed the patient's demand provides oxygen whose final concentration is tantamount to the FIO2 set initially[13]. Secondly, High flow rates with HFNC can create of a great oxygen reservoir in nasopharyngeal area and increase tidal volume[31, 32]. Thus, the oxygenation was greater in intervention group. Thirdly, there is an analysis demonstrating that higher pressures are obtained during expiration than inspiration, which are flow dependent[40]. It delivers a low level of positive airway pressure in expiratory phase[37] which transmits to the alveoli, contributing to lung compliance increment and end-expiratory lung volume increment[40]. Also, we found that with the prolongation of time, the improvement of blood oxygen saturation was greater. It is possible that the airway pressures initially are low and thus a longer time period is needed to recruit any atelectatic lung areas[45]. HFNC may cause a reduction in PaCO2, which has been confirmed in both stable and acute COPD[26]. This is attributed to the wash-out of CO2 in the upper airway and increment of tidal volume.

This study has some important limitations. First, the sample size was small and only a 72-hour clinical intervention was conducted. The long-term effect of HFNC needs to be further studied. Second, there are many subjective outcome measures, and more objective indicators are needed to verify the effect of HFNC. Third, patients and research personals could not be blinded to group assignment. However, the person who performed the statistical analysis were blinded.

This study demonstrated that HFNC is a kind of promising oxygen therapy in advanced cancer patients with dyspnea undergoing palliative treatment. HFNC can significantly improve the symptoms of dyspnea, dryness of mouth and sleep quality among patients with advanced cancer. Moreover, HFNC can effectively decrease RR, HR and PaCO2, while increase SpO2 and PaO2. Consequently, HFNC can be a useful respiratory support strategy in supporting advanced cancer patients to feel more comfortable.

Declarations

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Availability of data and material: All data can be available on https://www.chictr.org.cn/index.aspx

Code availability (software application or custom code): SPSS version 22.0(SPSS Inc., Chicago, IL, USA)

Authors' contributions: Conceptualization: [Zhaoning Xu, Pingping Li]; Methodology: [Zhaoning Xu, Pingping Li]; Formal analysis and investigation: [Zhaoning Xu, Pingping Li, Chi Zhang]; Writing - original draft preparation: [Zhaoning Xu, Pingping Li, Chi Zhang, Dedong Ma]; Writing - review and editing: [Zhaoning Xu, Pingping Li, Chi Zhang, Dedong Ma]; Funding acquisition: [Dedong Ma]; Supervision: [Dedong Ma]

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals: Not applicable

Ethics approval: All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The trial was approved by the first hospital of Zibo City in China Ethics Committee (No.2019016).

Consent to participate (include appropriate statements): Informed consent was obtained from all individual participants included in the study.

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Figures

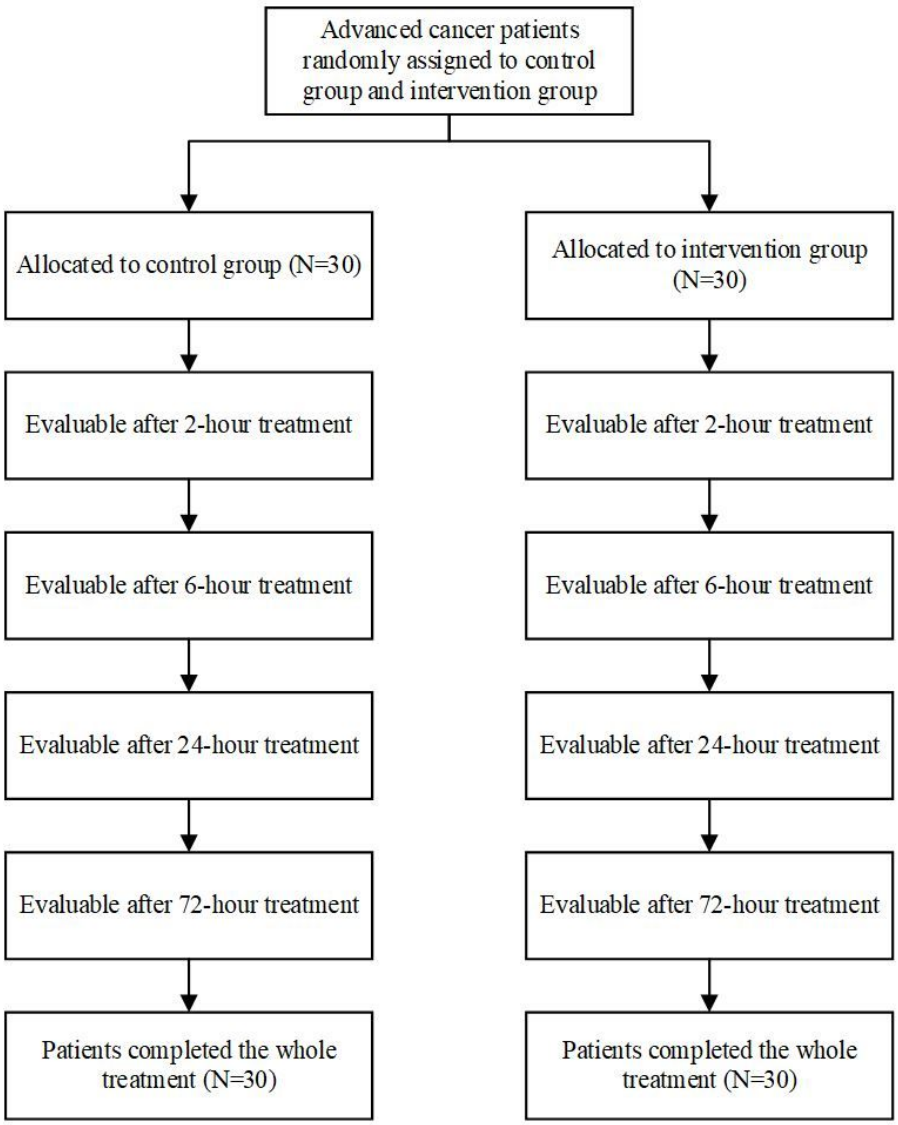

Figure 1

The participant flow diagram (Figure 1) shows that all the subjects completed the whole treatment. Post-hoc manifests 1-βcan reach 0.86 (effect size = 0, α=0.05).

Supplementary Files

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