High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Relieving Dyspnea in Emergency Palliative Patients With Do-Not-Intubate Status: A Randomized Crossover Study

Onlak Ruangsomboon, MD; Thawonrat Dorongthom, MD; Tipa Chakorn, MD*; Apichaya Monsomboon, MD; Nattakarn Praphruetkit, MD; Chok Limsuwat, MD; Usapan Surabenjawong, MD; Sattha Riyapan, MD; Tanyaporn Nakornchai, MD; Wansiri Chaisirin, MD

*Corresponding Author. E-mail: tipa102@yahoo.com.

Study objective: Palliative patients often visit the emergency department (ED) with respiratory distress during their end-of-life period. The goal of management is alleviating dyspnea and providing comfort. High-flow nasal cannula may be an alternative oxygen-delivering method for palliative patients with do-not-intubate status. We therefore aim to compare the efficacy of high-flow nasal cannula with conventional oxygen therapy in improving dyspnea of palliative patients with do-not-intubate status who have hypoxemic respiratory failure in the ED.

Methods: This randomized, nonblinded, crossover study was conducted with 48 palliative patients aged 18 years or older with do-not-intubate status who presented with hypoxemic respiratory failure to the ED of Siriraj Hospital, Bangkok, Thailand. The participants were randomly allocated to conventional oxygen therapy for 60 minutes, followed by high-flow nasal cannula for 60 minutes (n=24) or vice versa (n=24). The primary outcome was modified Borg scale score. The secondary outcomes were numeric rating scale score of dyspnea and vital signs.

Results: Intention-to-treat analysis included 44 patients, 22 in each group. Baseline mean modified Borg scale score was 7.6 (SD 2.2) (conventional oxygen therapy first) and 8.2 (SD 1.8) (high-flow nasal cannula first). At 60 minutes, mean modified Borg scale score in patients receiving conventional oxygen therapy and high-flow nasal cannula was 4.9 (standard of mean 0.3) and 2.9 (standard of mean 0.3), respectively (mean difference 2.0; 95% confidence interval 1.4 to 2.6). Results for the numeric rating scale score of dyspnea were similar to those for the modified Borg scale score. Respiratory rates were lower with high-flow nasal cannula (mean difference 5.9; 95% confidence interval 3.5 to 8.3), and high-flow nasal cannula was associated with a significantly lower first-hour morphine dose.

Conclusion: High-flow nasal cannula was superior to conventional oxygen therapy in reducing the severity of dyspnea in the first hour of treatment in patients with do-not-intubate status and hypoxemic respiratory failure. [Ann Emerg Med. 2020;75:615-626.]

Please see page 616 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.
Continuing Medical Education exam for this article is available at http://www.acep.org/ACEPeCME/.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2019.09.009

INTRODUCTION

Background

Patients with advanced diseases, especially those with diseases involving the lungs, often present to an emergency department (ED) with hypoxemic respiratory distress and even failure. Some of these patients are receiving palliative care and have preexisting do-not-intubate status, do-not-resuscitate (DNR) advanced care plans, or both. These palliative patients want to receive only comfort measures. Toward the end of their lives, the goal of treatment is primarily symptomatic relief. This poses a challenge for emergency physicians in regard to what measures are best to alleviate dyspnea for these patients.

Conventional oxygen therapy is used to improve oxygenation but may not effectively decrease dyspnea severity.[1-5] Although noninvasive ventilation may decrease severity of dyspnea in palliative patients,[6-9] it may not provide justifiable relief of symptoms for all of them,

Editor's Capsule Summary

What is already known on this topic

Palliative patients with do-not-intubate status may present to the emergency department (ED) in acute respiratory distress. Noninvasive ventilation is not desirable for these patients. High-flow nasal cannula is a novel treatment for acute dyspnea.

What question this study addressed

Does high-flow nasal cannula effectively reduce breathing discomfort in palliative care patients presenting to the ED with acute dyspnea?

What this study adds to our knowledge

In this randomized crossover trial of 48 patients in Thailand, high-flow nasal cannula provided greater dyspnea symptom relief than conventional oxygen therapy. Most patients preferred high-flow nasal cannula.

How this is relevant to clinical practice

High-flow nasal cannula offers an appealing option for alleviating acute respiratory distress in palliative patients.

especially for those with excessive secretion and decreased level of consciousness. The quality of mouth care and tolerability are also not optimal. Patients receiving noninvasive ventilation cannot eat or talk and may feel discomfort or experience complications from the noninvasive ventilation mask.[9] Positive pressure from noninvasive ventilation may also prolong the end-of-life discomfort of patients.

High-flow nasal cannula is an innovative cannula device delivering gases at flow rates from 30 to 60 L/min for adults and a constant Fio_2 at 0.21 to 1.0, decreasing anatomic dead space and thereby decreasing respiratory effort.[10,11] It also delivers gas warmed to 37°C (98.6°F) and is 100% humidified, providing more patient comfort.[10,11] High-flow nasal cannula compared with conventional oxygen therapy in ICUs could decrease dyspnea severity in hypoxemic respiratory failure of various causes.[10-14] It has also been effective in EDs for patients with all-cause hypoxemic respiratory failure and cardiogenic pulmonary edema.[15,16]

Importance

Better patient comfort, the primary goal for palliative patients, is a benefit of high-flow nasal cannula clearly observed in previous studies.[12-16] Observational studies of patients with do-not-intubate status in ICUs have reported decreased dyspnea and improved physiologic variables through the use of a high-flow nasal cannula.[17-19] However, to our knowledge no randomized controlled trial has investigated the efficacy of high-flow nasal cannula in improving dyspnea in palliative patients with do-not-intubate status who have hypoxemic respiratory failure in an ED setting.

Goals of This Investigation

The primary aim of this trial was to compare the efficacy of high-flow nasal cannula versus conventional oxygen therapy in the treatment of palliative patients with acute dyspnea.

MATERIALS AND METHODS

Study Design

We conducted a randomized, nonblinded, AB/BA crossover trial comparing conventional oxygen therapy and high-flow nasal cannula (Figure 1). The protocol was approved by Siriraj institutional review board. We did not make any changes to study protocol after trial registration.

Setting

We conducted the trial at the ED of Siriraj Hospital, the largest tertiary university hospital in Bangkok, Thailand, with greater than 20,000 ED visits annually. We recruited patients between November 2017 and August 2018, and we enrolled participants with informed consent obtained from either themselves or their next of kin. In our hospital, patients with advanced incurable diseases are referred to a palliative clinic, where the patients with their relatives in attendance are asked whether they want intubation or other life-sustaining management during their end-of-life period. If they agree to have do-not-intubate status, DNR status, or both, this statement is written in their electronic medical records, which emergency physicians can retrieve and follow.

Selection of Participants

Eligible participants were adults aged 18 years or older, with palliative status and known do-not-intubate status, who presented to our ED with hypoxemic respiratory failure, defined as an oxygen saturation by pulse oximetry (SpO_2) of less than 90% on room air, a respiratory rate greater than or equal to 30 breaths/min, accessory muscle use, and a modified Borg scale score greater than or equal to 4.[20,21] We excluded patients if they were not able to cooperate; had decreased level of consciousness, defined as a Kelly score[22] less than 4, and were not able to give answers

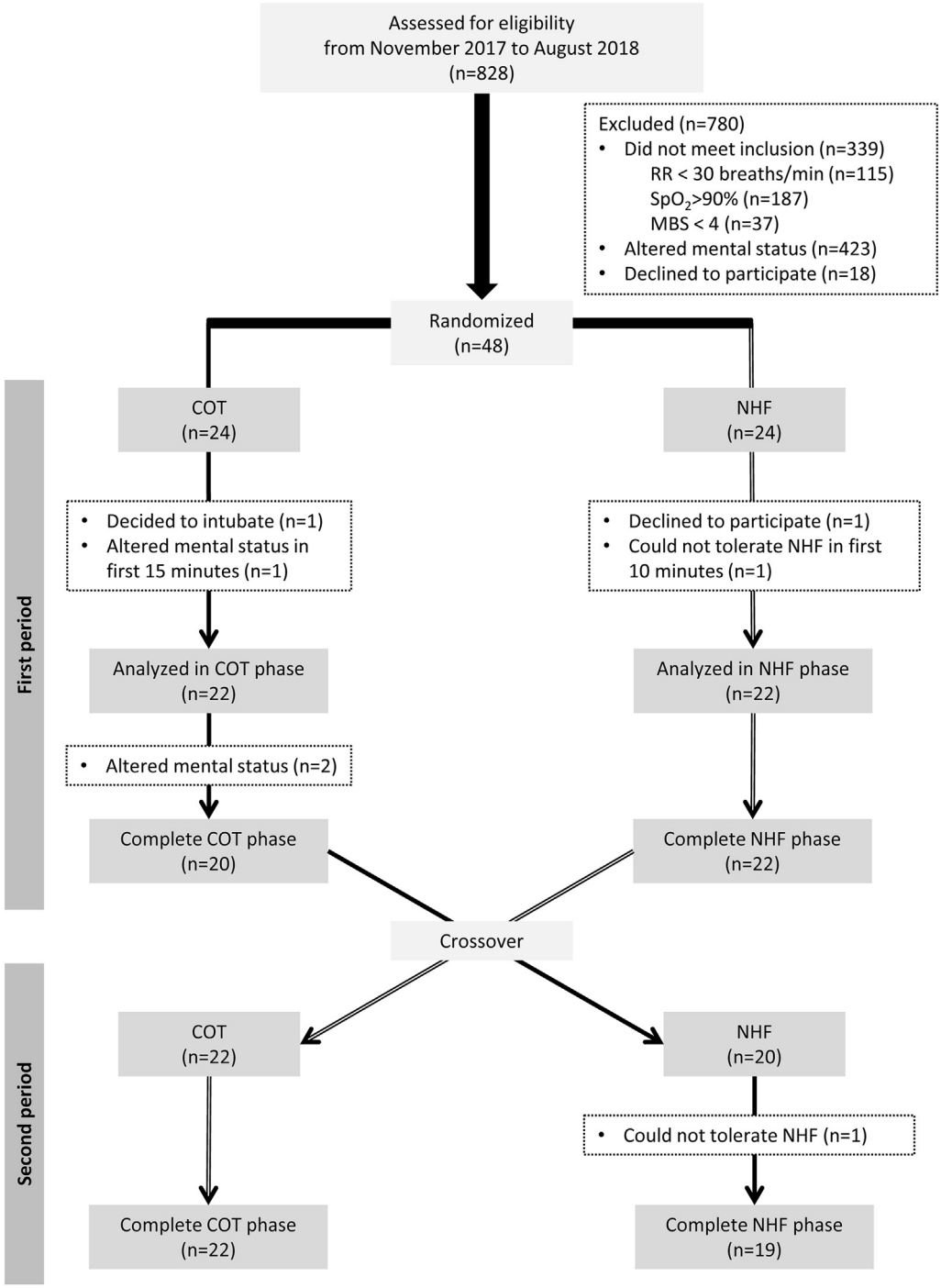

Figure 1. Design and flow of participants through the trial. *RR*, Respiratory rate; *MBS*, modified Borg scale; *COT*, conventional oxygen therapy; *HFNC*, high-flow nasal cannula.

to simple questions; or had contraindications for positive airway pressure devices.

Interventions

After patients arrived at the ED, an emergency physician assessed them consecutively for eligibility. This physician gave standard treatment, including conventional oxygen therapy, as required before the trial. This physician also notified a project investigator, who confirmed eligibility, enrolled the patient with informed consent, randomized the sequence of interventions, and completed data collection. We performed a computer-generated, mixed-block (block size of 2 and 4) randomization for sequence assignment (1:1 ratio), using sealed opaque envelopes.

We gave conventional oxygen therapy (treatment A) by nasal cannula or nonrebreather mask for 60 minutes. We gave high-flow nasal cannula (treatment B) by an Optiflow cannula using an AIRVO 2 humidified high-flow system (Fisher & Paykel Healthcare, Auckland, NZ) for 60 minutes. We set the initial high-flow nasal cannula flow rate at 35 L/min and adjusted it to between 30 and 60 L/min to improve the participant's comfort. We adjusted Fio_2 and conventional oxygen therapy oxygen flow rate to achieve a steady-state oxygen SpO_2 greater than or equal to 95% and maintained it for 60 minutes.

In accordance with the crossover design of the study, we randomly assigned patients to receive either conventional oxygen therapy for 60 minutes, immediately followed by high-flow nasal cannula for 60 minutes (AB), or vice versa (BA), with an active washout period[23] (Figure 1). We chose a crossover trial design because of the anticipated limited number of eligible and consenting palliative patients with do-not-intubate status who would be able to complete the study protocol, as well as the opportunity for the participants to choose their preferred intervention at the study's end. We did not perform a passive washout period because of ethical reasons and the assumed rapidity of washout of the effect of high-flow nasal cannula and conventional oxygen therapy.

During the trial, all participants received standard treatments and interventions to alleviate respiratory distress. We gave intravenous morphine if needed to reduce modified Borg scale score by at least 1 point to achieve a score of less than or equal to 5. Initially, the dose was a 2-mg bolus, followed by an infusion rate of 1 mg/hour, titratable to achieve the goal modified Borg scale score. After completing the trial, we continued high-flow nasal cannula or conventional oxygen therapy according to the participant's preference.

Outcome Measures

The primary aim was comparing the patient-reported dyspnea after each oxygen delivery method. The primary outcome was degree of dyspnea measured by the modified Borg scale score. This is a validated category ratio scale ranging from 0 to 10 points that uses category word descriptor anchors at various points on the scale to ensure the ratio scaling of answers (Appendix E1, available online at http://www.annemergmed.com).[20,21] The investigators asked the participants to rate by speaking or marking the score on a form.

The secondary aims were assessing validity of the primary aim outcome measured by another dyspnea rating scale, as well as comparing vital signs and inhospital mortality. The secondary outcomes were numeric rating scale score of dyspnea, effects on vital signs (ie, respiratory rate, SpO_2, pulse rate, and mean arterial pressure), high-flow nasal cannula–associated adverse event rate, and inhospital mortality rate.

We collected dyspnea scale scores and physiologic variables at the start of each intervention and at 15, 30, and 60 minutes after starting a trial intervention.

We also measured the numeric rating scale score of dyspnea, a validated dyspnea scale ranging from 0 ("no shortness of breath") to 10 ("worst shortness of breath") points.[24,25] Studies have validated both scales for rating dyspnea in palliative care,[26,27] and one clinical trial studying the use of high-flow nasal cannula in patients with advanced cancer used them.[19] Both scales were translated to Thai. We made no changes to the trial protocol after the trial commenced.

Primary Data Analysis

A previous randomized trial showed high-flow nasal cannula was noninferior to noninvasive ventilation in decreasing dyspnea in palliative patients,[19] and no previous trials to our knowledge have compared high-flow nasal cannula with conventional oxygen therapy in patients with do-not-intubate status and hypoxemic respiratory failure. Therefore, assuming the treatment effect of high-flow nasal cannula in the present study would be similar to that of a previous study comparing noninvasive ventilation with conventional oxygen therapy,[9] we considered a mean difference of modified Borg scale score of 1 point (SD 1.8) between the 2 groups to be significant.[9] Using a 2-sided type I error of 0.05 and 90% power, we needed a sample of 19 participants per group to complete the protocol. Accounting for a dropout rate of 25%, we calculated needing to enroll 24 patients in each sequence.

We performed all statistical analyses on an intention-to-treat basis. We presented continuous variables as mean (SD) or median (interquartile range) as appropriate. We described categoric variables as frequencies and percentages. We analyzed baseline differences between groups with Student's t test or Mann-Whitney U test for continuous variables as appropriate and χ^2 tests for categoric variables.

For the primary analysis, we constructed a linear mixed model with patient effects as random effects and the variables of treatment, period, time, treatment-by-time interaction, and carryover effect as fixed effects. The initial 15 minutes of each period was an active washout period that we did not analyze. Therefore, we used the

15-minutes values as the baseline and compared the values at 30 and 60 minutes only after starting the intervention. For missing data caused by early termination, we assumed they were missing at random and handled them by maximum likelihood estimation. We conducted sensitivity analyses by the linear mixed model,[28] adjusting for the baseline value of the outcome variable. We also adjusted for dosage of intravenous morphine during the first hour as a mediating factor. We furthermore performed sensitivity analysis as a parallel-group trial of the first period only. We performed all analyses with SAS Studio (version 9.2; SAS Institute, Inc., Cary, NC) and SPSS (version 18.0; SPSS, Chicago, IL).

RESULTS

Characteristics of Study Subjects

We randomized 48 of 828 patients assessed for eligibility (24 in each sequence). We excluded a total of 4 participants during the active washout of the first period. Therefore, these participants did not contribute any data to the analysis. We excluded 2 participants receiving conventional oxygen therapy from the conventional oxygen therapy–first group because of a decision to intubate early after the trial commenced (n=1) and altered mental status (n=1). We excluded 2 participants receiving high-flow nasal cannula from the high-flow nasal cannula–first group because of a decision not to participate (n=1) and intolerance to high-flow nasal cannula after using it for 10 minutes (n=1) (Figure 1). Therefore, a total of 44 participants (22 per group) remained in the intention-to-treat analysis. After the active washout of the first period, we excluded 2 participants receiving conventional oxygen therapy in the conventional oxygen therapy–first group in the first period because of altered mental status. In the second period, one participant receiving high-flow nasal cannula in the conventional oxygen therapy–first group could not tolerate high-flow nasal cannula (Figure 2*A*). Consequently, a total of 41 participants completed the study protocol (Figure 1).

Baseline characteristics of participants are presented in Table 1. The overall mean age was 60.3 years. Participants randomized into the conventional oxygen therapy–first treatment sequence were older. The most common disease for do-not-intubate status was malignancy (91.7%). Of these patients, 84.1% had metastasis, and 72.7% had lung involvement. Almost half of the recruited participants had previously been prescribed opioid (41.7%) and home oxygen therapy (45.8%). No participants had intravenous morphine prescribed before starting the trial. Vital signs of participants on ED arrival and at the start of intervention, as well as modified Borg scale score and numeric rating scale score of dyspnea at 0 minutes, were comparable between the treatment sequences. The 4 excluded participants (women n=2, advanced cancer n=4) had a mean age of 63.3 years and mean initial modified Borg scale score and numeric rating scale score of dyspnea of 8.1 and 7.8 points, respectively, and a mean respiratory rate of 35 breaths/min.

Each participant's modified Borg scale score at the end of each intervention and at each measured time is shown in Figure 2. There was no statistically significant carryover effect. After controlling for a significant period effect, mean modified Borg scale score at 60 minutes after starting high-flow nasal cannula was 2.9 (standard of mean [SE] 0.3) and mean modified Borg scale score with conventional oxygen therapy was 4.9 (SE 0.3) (mean difference 2.0; 95% confidence interval [CI] 1.4 to 2.6). At 30 minutes after initiation of a treatment, the mean modified Borg scale score with high-flow nasal cannula was also significantly lower than that with conventional oxygen therapy (3.8 [SE 0.3] versus 5.1 [SE 0.3], respectively; a mean difference of 1.3 [95% CI 0.7 to 1.9]). Sensitivity analyses adjusting for baseline values, adjusting for first-period intravenous morphine dosage, and a per-protocol analysis (n=41) showed similar results (Table 2). Evaluation of first-period data showed only that mean modified Borg scale scores at both 30 and 60 minutes after the start of high-flow nasal cannula were significantly lower than those of conventional oxygen therapy (Table 3).

Results similar to those with the mean modified Borg scale score were observed in the mean numeric rating scale of dyspnea. Mean respiratory rate was also significantly decreased during high-flow nasal cannula compared with conventional oxygen therapy (25.1 [SE 1.2] versus 30.9 [SE 1.2]; mean difference 5.9; 95% CI 3.5 to 8.3). Mean numeric rating scale score of dyspnea and mean respiratory rate were also significantly decreased at 30 minutes after the start of high-flow nasal cannula (Figure 3). SpO_2 increased and pulse rate decreased significantly more during high-flow nasal cannula compared with conventional oxygen therapy (Table 2).

Sensitivity analysis using only the first-period data showed that high-flow nasal cannula could significantly decrease mean numeric rating scale score of dyspnea and mean respiratory rate at 30 and 60 minutes after the start of treatment compared with conventional oxygen therapy. No between-group differences were found in SpO_2, pulse rate, and mean arterial pressure (Table 3). There were more patients needing intravenous morphine in the conventional oxygen therapy–first group compared with the high-flow

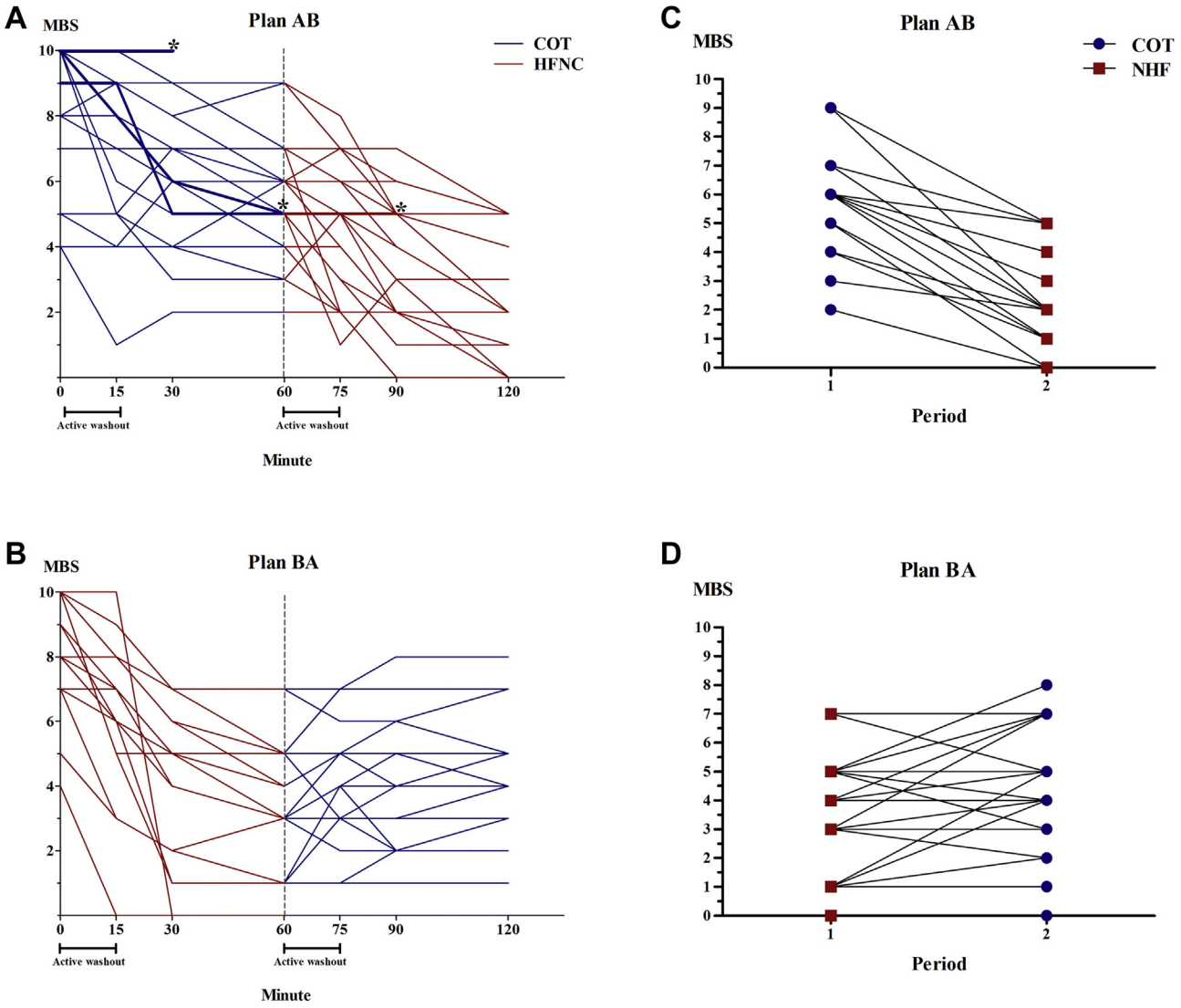

Figure 2. Changes in modified Borg scale score of each participant over time by plan (*A*, *B*) and at the end of each study period (*C*, *D*). The thick lines in *A* indicate patients who did not complete the protocol and asterisks indicate the points at which they exited the trial.

nasal cannula–first group (Table 1). First-period intravenous morphine dosage was also significantly higher in patients receiving conventional oxygen therapy compared with high-flow nasal cannula (mean difference 0.9; 95% CI 0.2 to 1.6) (Table 3).

Two patients (4.2%) could not tolerate high-flow nasal cannula because of discomfort. There were no serious or life-threatening complications associated with high-flow nasal cannula. Some minor complications included 5 participants reporting discomfort and 2 complaining of feeling hot after using high-flow nasal cannula. The majority of per-protocol participants (78%) preferred to continue using high-flow nasal cannula after the study period, continuing to receive it for a median duration of 5.5 hours. The mortality rate was 17.7% and 65.9% at ED and hospital discharge, respectively (Table 1).

LIMITATIONS

There were some limitations of the present study. First, the lack of any blinding to the devices used may have biased outcomes measured. Second, intravenous morphine could have caused an assumed carryover effect. However, we found no carryover effect in the analysis. Furthermore, the sensitivity analysis using only first-period modified Borg scale score data still showed a superior treatment effect of high-flow nasal cannula compared with conventional oxygen therapy. Third, we did not compare high-flow nasal cannula with noninvasive ventilation, which might be a

Table 1. Characteristics of patients.

Characteristic	COT First (n=24)	HFNC First (n=24)	Total (n=48)
Variable at baseline			
Age, mean (SD)	66.7 (9.6)	54 (13.1)	60.3 (13.1)
Female sex)	15 (62.5)	12 (50.0)	27 (56.3)
Underlying diseases			
Malignancy*	22 (91.7)	22 (91.7)	44 (91.7)
Metastasis	19 (86.4)	18 (81.8)	37 (84.1)
Lung or pleural involvement	17 (77.3)	15 (68.2)	32 (72.7)
Chronic lung disease	4 (16.6)	1 (4.2)	5 (10.4)
Previous opioid use	8 (33.3)	12 (50.0)	20 (41.7)
Morphine-equivalent dose, mean (SD), mg/day	25 (10.7)	55 (65.9)	43 (52.8)
Home oxygen therapy	11 (45.8)	11 (45.8)	22 (45.8)
Duration before intervention, min	75 [154]	75 [157]	75 [144]
Type of oxygen therapy before intervention			
Cannula	6 (25.0)	6 (25.0)	12 (25.0)
Nonrebreather mask	18 (75.0)	18 (75.0)	36 (75.0)
Oxygen flow before intervention, mean (SD)	8.3 (2.6)	8.7 (2.5)	8.5 (2.6)
Initial vital signs, mean (SD)			
Respiratory rate, breaths/min	32.8 (7.5)	34.1 (8.8)	33.4 (8.1)
Pulse oximetry	89.5 (9.0)	89.0 (9.6)	89.2 (9.2)
Pulse rate, beats/min	115.0 (17.1)	116.7 (29.2)	115.9 (23.8)
Mean arterial pressure, mm Hg	93.4 (19.3)	89.9 (15.6)	91.6 (17.1)
Parameter before intervention, mean (SD)			
Modified Borg scale score	7.6 (2.2)	8.2 (1.8)	7.9 (2.0)
Numeric rating scale score	7.6 (2.2)	8.1 (1.8)	7.8 (2.0)
Respiratory rate, breaths/min	37.0 (9.0)	35.3 (7.0)	36.2 (8.0)
Pulse oximetry	92.9 (6.7)	90.2 (7.0)	91.6 (6.9)
Pulse rate, beats/min	116.8 (17.2)	115.6 (24.2)	116.2 (20.7)
Mean arterial pressure, mm Hg	90.4 (17.8)	84.6 (19.4)	87.5 (18.6)
Variables after study intervention	**COT first (n=22)**	**HFNC first (n=22)**	**Total (n=44)**
COT, mean (SD)			
Oxygen flow, L/min	8.5 (2.7)	8.7 (2.5)	8.6 (5.4)
HFNC, mean (SD)			
Gas flow, L/min	34.1 (5.2)	37.5 (5.3)	35.8 (5.4)
Fraction of inspired oxygen	0.7 (1.7)	0.7 (0.2)	0.7 (0.2)
Temperature, °C	34.3 (2.1)	34.5 (2.0)	34.4 (2.0)
Cointervention			
None	14 (63.6)	15 (68.2)	29 (65.9)
Bronchodilator	5 (22.7)	7 (31.8)	12 (27.3)
Thoracocentesis	1 (4.5)	—†	1 (2.3)
Dexamethasone	2 (9.1)	—	2 (4.5)
First-period cointervention			
None	16 (72.7)	16 (72.7)	32 (72.7)
Bronchodilator	4 (18.2)	6 (27.3)	10 (22.7)
Dexamethasone	2 (9.1)	—	2 (4.5)
Patients receiving IV morphine in the first hour, mean (SD)	13 (59.1)	6 (27.3)	19 (43.2)
First-hour dosage, mg/h	1.4 (1.4)	1.0 (0.2)	1.0 (1.3)

Table 1. Continued.

Variables after study intervention	COT first (n=22)	HFNC first (n=22)	Total (n=44)
Patients receiving IV morphine in the second hour, mean (SD)	8 (36.4)	6 (27.3)	14 (31.8)
Second-hour dosage, mg/h	0.8 (1.4)	0.5 (0.2)	0.7 (1.2)
Death at discharge	16 (72.7)	13 (59.1)	29 (65.9)

IV, Intravenous.
Data are presented as No. (%) or median [IQR] unless otherwise indicated.
*Total n of metastasis=44, including for COT first n=22 and n for HFNC first n=22.
†Dashes indicate that no patients were given the respective cointervention.

Table 2. Primary outcome and secondary outcomes.

	At 30 Minutes			At 60 Minutes		
Study Outcome	**COT (n=22)**	**HFNC (n=22)**	**Difference of COT Minus HFNC (95% CI)**	**COT (n=22)**	**HFNC (n=22)**	**Difference of COT Minus HFNC (95% CI)**
Modified Borg scale						
Primary*	5.1 (0.3)	3.8 (0.3)	1.3 (0.7 to 1.9)	4.9 (0.3)	2.9 (0.3)	2.0 (1.4 to 2.6)
Baseline adjusted†	5.1 (0.2)	3.8 (0.2)	1.3 (0.7 to 1.9)	4.8 (0.2)	2.9 (0.2)	1.9 (1.3 to 2.5)
Morphine adjusted‡	5.0 (0.2)	3.8 (0.2)	1.2 (0.6 to 1.8)	4.8 (0.2)	2.9 (0.2)	1.9 (1.3 to 2.5)
Per protocol§	5.0 (0.3)	3.7 (0.3)	1.3 (0.7 to 1.9)	4.8 (0.3)	2.8 (0.3)	2.0 (1.4 to 2.6)
Numeric rating scale						
Primary*	5.2 (0.3)	3.9 (0.3)	1.3 (0.7 to 1.9)	5.1 (0.3)	2.9 (0.3)	2.2 (1.6 to 2.9)
Baseline adjusted†	5.2 (0.3)	3.9 (0.3)	1.3 (0.7 to 1.9)	5.1 (0.3)	2.9 (0.3)	2.2 (1.6 to 2.9)
Morphine adjusted‡	5.1 (0.3)	3.9 (0.3)	1.2 (0.6 to 1.8)	5.0 (0.3)	3.0 (0.3)	2.0 (1.4 to 2.6)
Per protocol§	5.2 (0.3)	3.8 (0.3)	1.4 (0.8 to 2.0)	5.1 (0.3)	2.9 (0.3)	2.2 (1.6 to 2.9)
Respiratory rate, breaths/min						
Primary*	31.3 (1.0)	26.8 (1.1)	4.4 (2.6 to 6.2)	30.9 (1.2)	25.1 (1.2)	5.9 (3.5 to 8.3)
Baseline adjusted†	30.6 (0.5)	27.7 (0.6)	2.9 (1.7 to 4.1)	30.2 (0.9)	25.9 (0.9)	4.2 (1.8 to 6.6)
Morphine adjusted‡	30.6 (0.5)	27.7 (0.6)	2.9 (1.7 to 4.1)	30.2 (0.9)	25.9 (1.2)	4.3 (1.9 to 6.7)
Per protocol§	31.2 (1.1)	26.6 (1.1)	4.6 (2.8 to 6.4)	31.4 (1.2)	24.9 (1.2)	6.5 (4.3 to 8.7)
Pulse oximetry						
Primary*	97.6 (0.4)	98.2 (0.4)	−0.6 (−1.4 to 0.2)	96.9 (0.5)	98.2 (0.5)	−1.3 (−2.3 to −0.3)
Baseline adjusted†	97.8 (0.2)	98.0 (0.2)	−0.2 (−0.8 to 0.4)	97.1 (0.4)	98.0 (0.4)	−0.9 (−1.9 to 0.1)
Morphine adjusted‡	97.8 (0.2)	98.0 (0.2)	−0.2 (−0.8 to 0.4)	97.1 (0.4)	98.0 (0.4)	−0.9 (−1.9 to 0.1)
Per protocol§	97.6 (0.5)	98.2 (0.5)	−0.6 (−1.4 to 0.2)	97.1 (0.5)	98.2 (0.5)	−1.1 (−2.1 to −0.1)
Pulse rate, beats/min						
Primary*	113.1 (2.7)	108.6 (2.7)	4.5 (1.6 to 7.4)	113.0 (2.7)	109.0 (2.7)	3.9 (1.5 to 6.3)
Baseline adjusted†	112.0 (1.0)	110.4 (1.0)	1.6 (−0.9 to 3.1)	111.9 (1.1)	110.9 (1.1)	1.0 (−1.9 to 3.9)
Morphine adjusted‡	112.0 (1.0)	110.5 (1.0)	1.5 (−1.0 to 4.0)	111.8 (1.0)	111.0 (1.1)	0.9 (−2.0 to 3.8)
Per protocol§	114.3 (2.8)	109.6 (2.8)	4.7 (1.8 to 7.6)	114.1 (2.7)	110.1 (2.7)	4.0 (1.5 to 6.5)
Mean arterial pressure, mm Hg						
Primary*	80.9 (2.1)	74.4 (2.1)	3.4 (−0.5 to 7.3)	80.8 (2.1)	78.6 (2.0)	2.2 (−1.7 to 6.1)
Baseline adjusted†	79.6 (1.1)	79.2 (1.1)	0.3 (−2.8 to 3.4)	79.5 (1.6)	80.4 (1.7)	−0.9 (−5.6 to 3.8)
Morphine adjusted‡	79.6 (1.1)	79.2 (1.1)	0.4 (−2.7 to 3.5)	79.5 (1.1)	80.4 (1.7)	−0.9 (−5.6 to 3.8)
Per protocol§	81.5 (2.1)	77.7 (2.1)	3.8 (−0.1 to 7.7)	81.6 (2.1)	78.9 (2.1)	2.7 (−1.2 to 6.6)

Data are presented as mean (SE).
*Unadjusted primary analysis.
†Analysis adjusted for baseline values of that outcome variable.
‡Adjusted for intravenous morphine dosage.
§Total N for per-protocol analysis=41, including for COT first n=19 and for HFNC first n=22.

Table 3. Outcomes of the first period only.

Study Outcome	COT (n=22)	HFNC (n=22)	Difference (95% CI)
Modified Borg Scale			
15 min	6.8 (2.4)	6.1 (2.4)	0.7 (−0.8 to 2.2)
30 min	6.3 (2.0)	4.1 (2.4)	2.2 (0.8 to 3.5)
60 min*	5.6 (1.8)	3.3 (2.0)	2.3 (1.1 to 3.5)
Numeric rating scale			
15 min	6.6 (2.2)	6.1 (2.4)	0.8 (−0.6 to 2.2)
30 min	6.4 (1.7)	4.2 (2.4)	2.2 (1.0 to 3.5)
60 min*	5.9 (1.5)	3.5 (2.1)	2.5 (1.3 to 3.6)
Respiratory rate, breaths/min			
15 min	33.9 (9.2)	29.6 (5.1)	0.8 (−0.8 to 8.2)
30 min	32.8 (9.0)	27.2 (5.2)	2.2 (1.1 to 10.0)
60 min	31.9 (9.3)	26.0 (3.7)	2.5 (1.6 to 10.0)
Pulse oximetry			
60 min	97.4 (3.7)	98.1 (2.1)	−0.7 (−2.5 to 1.1)
Pulse rate			
60 min	112.5 (16.5)	111.0 (20.1)	−0.7 (−9.7 to 12.7)
Mean arterial pressure			
60 min	83.5 (17.4)	77.3 (12.7)	6.2 (−3.1 to 15.4)
IV morphine in the first hour, mg/h	1.4 (1.4)	1.0 (0.2)	0.9 (0.2 to 1.6)

Data are presented as mean (SD).
*COT (n=21) because of exclusion of 1 participant for altered mental status after the 30-minute observation and HFNC (n=22).

more widely used oxygen-delivering method for this condition. However, in our experience, noninvasive ventilation was suboptimal in delivering comfort for this group of patients.

The generalizability of this study may be limited for many reasons. First, it was a single-center study. Second, the definition of the included participants was limited to patients with known palliative status and preexisting orders to receive only comfort measures, which might be different from palliative settings in other hospitals and countries. Third, we focused only on patients with respiratory failure and not those with a less severe degree of respiratory distress.

Although no carryover effect was observed and period effect was controlled for in the primary analysis, a crossover study might not be a suitable design for patients with actively progressing conditions. Parallel-group randomized controlled trials with larger sample sizes should be conducted to confirm our findings. Comparison between high-flow nasal cannula and noninvasive ventilation should also be further investigated.

DISCUSSION

Respiratory distress is one of the most common presenting symptoms in the ED. Palliative care patients with do-not-intubate status are predominantly treated for symptomatic relief rather than offered an attempt to improve physiologic parameters or reverse underlying causes. Although noninvasive ventilation may be the only alternative to intubation, it may not effectively deliver comfort, which is the goal of treatment for this patient group. In this randomized crossover trial, use of high-flow nasal cannula was associated with decreased dyspnea compared with conventional oxygen therapy, assessed primarily by mean modified Borg scale score, as well as mean numeric rating scale score of dyspnea and mean respiratory rate at 60 minutes after initiating treatment.

High-flow nasal cannula is an innovative oxygen-delivering device that can decrease respiratory effort and provide comfort.[11-14] It may serve as a novel approach toward better end-of-life care for palliative patients with respiratory distress and failure. Although studied in patients with acute hypoxemic respiratory failure of various causes, high-flow nasal cannula has limited evidence in regard to its use in end-of-life patients or palliative care. Retrospective observational studies in cancer patients and those with do-not-intubate status who are receiving high-flow nasal cannula have reported increased patient comfort, increased oxygenation, and decreased respiratory rate.[17,18] One randomized trial in

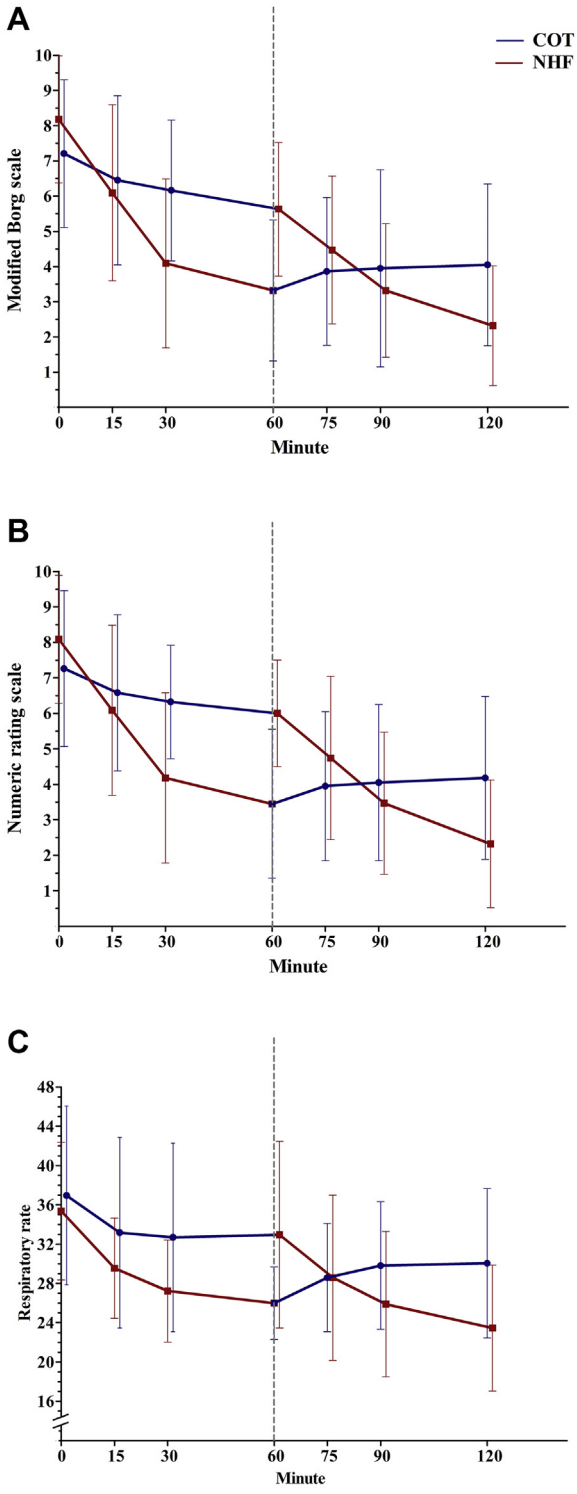

Figure 3. Changes in the primary and secondary outcomes over time.

patients with advanced cancer found high-flow nasal cannula was noninferior to noninvasive ventilation in improving dyspnea, respiratory rate, and oxygen saturation,[19] and a retrospective observational study reported comparable survival rate but better tolerance of high-flow nasal cannula over noninvasive ventilation.[28] However, all of these previous studies were either retrospective and nonrandomized or were conducted in ICUs. The inclusion criteria of those studies were also different from ours. We primarily focused on palliative patients with do-not-intubate status and respiratory failure, irrespective of their life expectancy. To our knowledge, the present study is the first randomized controlled trial of high-flow nasal cannula versus conventional oxygen therapy in palliative patients with do-not-intubate status and hypoxemic respiratory failure in an ED, where management to palliate the symptoms is often initiated.

In the present study, vital signs were significantly more improved in participants receiving high-flow nasal cannula compared with conventional oxygen therapy. These findings were similar to those of previous trials in palliative patients.[18,19] The present study adds to the body of evidence that high-flow nasal cannula can decrease the degree of dyspnea. The results of the present study were similar to those of the previous trials conducted in our ED, both of which also demonstrated early improvement in respiratory rate as early as 15 minutes after application of the device.[15,16] Taking those studies and the present study together, we therefore suggest that high-flow nasal cannula has beneficial effects at least within the first 30 minutes after device application, which is highly favorable for emergency settings. The effect of high-flow nasal cannula on patient comfort was also evidenced by the reduced quantity of analgesia (morphine) required during the first period. This result was concordant with that of a previous study reporting a lower dosage of morphine in end-of-life patients receiving noninvasive ventilation for dyspnea compared with those receiving conventional oxygen therapy.[9] Indeed, 2 participants discontinued because of altered mental status at 30 and 60 minutes while receiving conventional oxygen therapy in the first period, which may have been contributed to by the morphine given in the same period. Moreover, high-flow nasal cannula was well tolerated by most of the participants, and they preferred to continue with high-flow nasal cannula after the present study, as was the case in previous studies.[13,14,16,29] However, 2 participants in the present study could not tolerate high-flow nasal cannula because of discomfort caused by the high flow. Despite this, the proportion of participants who could not tolerate high-flow nasal cannula in the present study was very low, which is similar to findings in previous studies.[16,19] Consequently, it may be an option for an

oxygen delivery device with possible benefit over conventional oxygen therapy and noninvasive ventilation for palliative patients with do-not-intubate status and hypoxemic respiratory failure.

In conclusion, high-flow nasal cannula may decrease the degree of dyspnea more than conventional oxygen therapy and could be an option for an oxygen delivery method for palliative patients with do-not-intubate status and hypoxemic respiratory failure in the ED.

The authors acknowledge the assistance of Chulaluk Komoltri, PhD, for supervising the statistical analysis.

Supervising editor: Henry E. Wang, MD, MS. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Author contributions: OR and TC conceived the study, designed the trial, and supervised the conduct of the trial and data collection. All authors recruited the patients and managed the data, including quality control. OR analyzed the data and drafted the article. OR takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist. This study was funded by a grant from the Siriraj Research and Development Fund.

Publication dates: Received for publication June 17, 2019. Revisions received August 3, 2019, and August 25, 2019. Accepted for publication September 13, 2019. Available online December 19, 2019.

Trial registration number: TCTR 20171107001

Fisher & Paykel Healthcare provided the high-flow nasal cannula devices, which were Optiflow cannula and AIRVO 2 machines. The company played no role in the trial design, data collection, data analysis, or article preparation.

REFERENCES

1. Bruera E, de Stoutz N, Velasco-Leiva A, et al. Effects of oxygen on dyspnea in hypoxemic terminal-cancer patients. *Lancet*. 1993;342:13-14.
2. Booth S, Kelly MJ, Cox NP, et al. Does oxygen help dyspnea in patients with cancer? *Am J Respir Crit Care Med*. 1996;153:1515-1518.
3. Bruera E, Sweeney C, Willey J, et al. A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. *Palliat Med*. 2003;17:659-663.
4. Philip J, Gold M, Milner A, et al. A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. *J Pain Symptom Manage*. 2006;32:541-550.
5. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnea: a double-blind, randomized controlled trial. *Lancet*. 2010;376:784-793.
6. Cuomo A, Conti G, Delmastro M, et al. Noninvasive mechanical ventilation as a palliative treatment of acute respiratory failure in patients with end-stage solid cancer. *Palliative Med*. 2004;18:602-610.
7. Levy M, Tanios MA, Nelson D, et al. Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. *Crit Care Med*. 2004;32:2002-2007.
8. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive pressure ventilation reverses acute respiratory failure in select "do-not-intubate" patients. *Crit Care Med*. 2005;33:1976-1982.
9. Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomized feasibility trial. *Lancet Oncol*. 2013;14:219-227.
10. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55:408-413.
11. Dysart K, Miller TL, Wolfson MR, et al. Research in high flow therapy: mechanisms of action. *Respir Med*. 2009;103:1400-1405.
12. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. *Respir Care*. 2016;61:529-541.
13. Roca O, Hernandez G, Diaz-Lobato S, et al. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. *Crit Care*. 2016;20:109.
14. Helviz Y, Einav S. A systematic review of the high-flow nasal cannula for adult patients. *Crit Care*. 2018;22:71.
15. Rittayamai N, Tscheikuna J, Praphruetkit N, et al. Use of high-flow nasal cannula for acute dyspnea and hypoxemia in the emergency department. *Respir Care*. 2015;60:1377-1382.
16. Makdee O, Monsomboon A, Surabenjawong U, et al. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. *Ann Emerg Med*. 2017;70:465-472.
17. Epstein AS, Hartridge-Lambert SK, Ramaker JS, et al. Humidified high-flow nasal oxygen utilization in patients with cancer at Memorial Sloan-Kettering Cancer Center. *J Palliat Med*. 2011;14:835-839.
18. Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. *Respir Care*. 2013;58:597-600.
19. Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage*. 2013;46:463-473.
20. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.
21. Burdon JG, Juniper EF, Killian KJ, et al. The perception of breathlessness in asthma. *Am Rev Respir Dis*. 1982;126:825-828.
22. Kelly BJ, Matthay G. Prevalence and severity of neurological dysfunction in critically ill patients. Influence on need for continued mechanical ventilation. *Chest*. 1993;104:1818-1824.

23. Senn SJ. *Cross-over Trials in Clinical Research*. 2nd ed. Chichester, England: Wiley; 2002.
24. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. *Am J Crit Care*. 1998;7:200-204.
25. Wilcock A, Crosby V, Clarke D, et al. Repeatability of breathlessness measurements in cancer patients. *Thorax*. 1999;54:375.
26. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? a systematic review. *Palliat Med*. 2007;21:177-191.
27. Johnson MJ, Close L, Gillon SC, et al. Use of the modified Borg scale and numerical rating scale to measure chronic breathlessness: a pooled data analysis. *Eur Respir J*. 2016;47:1861-1864.
28. Jones B, Kenward MG. *Design and Analysis of Cross-Over Trials*. 3rd ed. Boca Raton, FL: CRC; 2003.
29. Koyauchi T, Hasegawa H, Kanata K, et al. Efficacy and tolerability of high-flow nasal cannula oxygen therapy for hypoxemic respiratory failure in patients with interstitial lung disease with do-not-intubate orders: a retrospective single-center study. *Respiration*. 2018;96:323-329.

IMAGES IN EMERGENCY MEDICINE

(continued from p. 577)

DIAGNOSIS:

Organoaxial gastric volvulus. Abdominal radiographs revealed a massively distended stomach with an air fluid level concerning for gastric outlet obstruction. A nasogastric tube was placed for gastric decompression, and an upper gastrointestinal series demonstrated a dilatated proximal stomach and no contrast emptying. Furthermore, the rotation of the stomach was abnormal (Figure 3). The pylorus and small bowel were never visualized. The patient was taken to the operating room for diagnostic laparoscopy. An organoaxial gastric volvulus without necrosis or perforation was appreciated. The volvulus was reduced and gastropexy with gastrostomy tube placement was performed without complication.

Acute gastric volvulus in the pediatric population is extremely rare.[1-4] Without a high index of suspicion and prompt surgical intervention, the mortality can be as high as 80%.[5] The classic appearance of organoaxial gastric volvulus on an abdominal radiograph is an "upside-down stomach," in which the stomach rotates on a longitudinal access, resulting in the greater curvature resting superior to the lesser curvature (Figure 3).[6,7] Definitive diagnosis is made with an upper gastrointestinal series, which reveals the gastric rotation and degree of obstruction.[2] Ultimately, the patient should be taken to the operating room urgently for reduction and prevention of complications, including gastric necrosis, peritonitis, shock, and death.[6]

Author affiliations: From the Department of Pediatric Emergency Medicine (Jones, Adams), Department of Diagnostic Radiology (Metz), and Department of Pediatric Surgery (Akay), Beaumont Health, Royal Oak, MI; and the Oakland University William Beaumont School of Medicine, Royal Oak, MI (Jones, Adams, Metz, Akay).

REFERENCES

1. Mirza B, Ijaz L, Sheikh A. Gastric volvulus in children: our experience. *Indian J Gastroenterol*. 2012;31:258-262.
2. Porcaro F, Mattioli G, Romano C. Pediatric gastric volvulus: diagnostic and clinical approach. *Case Rep Gastroenterol*. 2013;7:63-68.
3. Tillman BW, Merritt NH, Emmerton-Coughlin H, et al. Acute gastric volvulus in a six-year-old: a case report and review of the literature. *J Emerg Med*. 2013;46:191-196.
4. Al-Salem A. Acute and chronic gastric volvulus in infants and children: who should be treated surgically? *Pediatr Surg Int*. 2007;23:1095-1099.
5. Gerstle J, Chiu P, Emil S. Gastric volvulus in children: lessons learned from delayed diagnosis. *Semin Pediatr Surg*. 2009;18:98-103.
6. Cribbs RK, Gow KW, Wulkan ML. Gastric volvulus in infants and children. *Pediatrics*. 2008;122:e752-e762.
7. Park WH, Choi S, Suh S. Pediatric gastric volvulus: experience with 7 cases. *J Korean Med Sci*. 1992;7:258-263.