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ORIGINAL RESEARCH

Randomised control trial of humidified high flow nasal cannulae *versus* standard oxygen in the emergency department

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Abstract

***Objectives*:** The aim of the study was to determine if oxygen delivered through humidified high flow nasal cannulae (HHFNC) reduced the need for escalation in ventilation management and work of breathing in the ED patients presenting with acute undifferentiated shortness of breath compared with standard oxygen therapy.
***Methods*:** This was an unblinded randomised control trial conducted at two hospital EDs in Sydney, Australia. Eligible patients presenting with shortness of breath were randomised to HHFNC or standard oxygen therapy. Primary outcomes were the need to escalate ventilation therapy or a reduction in respiratory rate of 20% or more within 2 h of commencement.
***Results*:** One hundred patients were enrolled in the trial. The intervention group receiving HHFNC was associated with a higher proportion of patients with a reduced respiratory rate at 2 h (66.7% *vs* 38.5%, $P = 0.005$) and a lower proportion of patients requiring escalation in ventilation therapy (4.2% *vs* 19%, $P = 0.02$) compared with standard oxygen therapy.
***Conclusions*:** The use of high flow nasal cannula oxygenation was associated with improved respiratory state in selected patients presenting to the ED with acute undifferentiated shortness of breath.

Key words: *emergency department, oxygen, shortness of breath.*

Key findings

- Oxygen delivery via HHFNC has been used in a number of critical care settings as an alternative to NIV.
- There are few published reports investigating the use of HHFNC in the ED patients presenting with acute undifferentiated shortness of breath.
- In this randomised control trial, use of HHFNC was associated with improvements in respiratory state, including respiratory rate, dyspnoea scores and reduced need for NIV.

Introduction

Dyspnoea or shortness of breath is a common presentation to the EDs. The indications for oxygen therapy are to correct hypoxaemia and alleviate breathlessness.[1] Unassisted oxygen delivery devices include nasal cannulae or face masks and assisted ventilation devices commonly used in ED include non-invasive ventilation (NIV), such as Bilevel Positive Airway Pressure, Continuous Positive Airway Pressure and invasive ventilation.[1,2]

Over the past 10 years, there have been important changes in clinical guidelines around the use of oxygen and its administration. The changes have included the use of new targeted saturation ranges of 94–98% for the majority of patients and 88–92% for patients at risk of hypercapnia.[3] There have also been specific changes with respect to conditions, such as acute coronary syndrome, with the National Heart Foundation now recommending oxygen therapy only be administered when oxygen saturations are less than 93% with evidence of shock.[4]

Humidified high flow nasal cannulae (HHFNC) are a recently developed form of oxygenation that combines flow titration, humidification, heat and positive pressure. HHFNC allows for flows from 2 L up to 60 L; this is titrated according to the patient's work of breathing. The flow rates decreases oxygen dilution in the respiratory tract by reducing anatomical dead space and provides up to 5 cm H_2O positive pressure with a closed mouth.[5,6] Additionally, specific and accurate fraction of inspired oxygen (FiO_2) of 21–100% can be set and titrated according to the patient's targeted oxygen saturation range. Heat humidification is believed to assist with patient comfort and clearance of respiratory tract secretions.[7,8]

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TABLE 1. *Inclusion/exclusion criteria*

Inclusion	Exclusion
>16 years of age	Patients requiring immediate non-invasive ventilation or intubation
Complaining of 'shortness of breath'	Trauma patients
Respiratory rate ≥ 25	Suspected pneumothorax
SpO_2 ≤93%	Inability to provide consent • Altered mental state • Dementia • Developmentally delayed • Intoxicated • Mental health/delirium

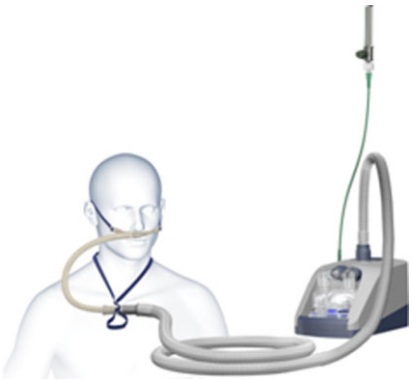

Figure 1. *AIRVO2, Optiflow, Fisher & Paykel, Auckland, New Zealand.*

The use of HHFNC has been reported in critical care settings,[9,10] including neonatal and adult intensive care units (ICUs) and postoperative units. To date, there is limited evidence on the use of HHFNC in patients presenting to ED with acute undifferentiated shortness of breath or which patients benefit most from the therapy. The aim of this study was to determine if HHFNC reduces the work of breathing and need for escalation in ventilation management in ED patients presenting with acute undifferentiated shortness of breath.

Methods

Study design

The study was an unblinded prospective randomised control trial.

Study population

Between December 2013 and March 2015, a convenience sample of patients was recruited from two hospital EDs – a tertiary referral hospital with greater than 73 000 emergency presentations per annum, and a level 4 metropolitan district hospital with around 40 000 emergency presentations per annum. The inclusion exclusion criteria study are summarised in Table 1. Eligible patients were identified by the treating nurse in the resuscitation or acute bed areas of the EDs. Adult patients presenting with shortness of breath who had both a respiratory rate (RR) >25 breaths per minute and oxygen saturations <93% as measured by the treating ED nurse, for whom non-invasive or invasive ventilation was not felt to be immediately indicated, were enrolled into the study. The decision regarding the use of NIV was at the discretion of the treating medical officer in ED.

Randomisation

Consenting patients were randomised to either the HHFNC group or standard oxygen therapy group, using an opaque envelope system based on a computer-generated random number sequence.

Intervention

Participants randomised to the intervention group were commenced on 50 L of flow with an FiO_2 of 30% delivered using a dedicated high flow delivery system (AIRVO2, Optiflow, Fisher & Paykel, Auckland, New Zealand; Fig. 1).

Participants randomised to the control group were commenced on standard nasal prongs or face mask (Hudson, venturi system or non-rebreather) at the discretion of the treating doctor and nurse. Oxygen therapy in both groups was then titrated over a 2 h period depending on the patient's condition and their response to treatment.

Patient characteristics were collected as well as baseline RR, oxygen saturations, heart rate and patient's self-reported dyspnoea score using the modified Borg scale, device and settings, venous blood gas results and the patient's perceived level of comfort according to the nurse treating the patient using a 5 point Likert scale. The modified Borg scale was a validated self-reported dyspnoea scale out of 10 with a higher score denoting more severe patient reported dyspnoea.[11,12] Patient self-reported comfort was assessed at the 1 h interval on a one-item scale from 1 (very uncomfortable) to 5 (very comfortable). Venous blood gas pH was routinely taken from the patient's intravenous cannula on presentation to ED.

Primary outcomes

The primary outcomes were either a reduction in the patient's RR by 20% within 2 h, or an escalation in ventilation requirements (i.e. increase to HHFNC or NIV or intubation) within 2 h from the time of commencement of therapy. These were assessed and measured by the treating nurse in ED.

Secondary outcomes

Other outcomes of interest were any reduction in the self-reported Borg score within 2 h of commencement of treatment, self-reported comfort score at 1 h post commencement of oxygen therapy, disposition from ED (admission to ward, ICU, or discharge from ED), and length of stay in ED.

Statistical analysis

Analysis was by intention to treat. Baseline characteristics were compared using standard descriptive statistics. The study hypothesis was that

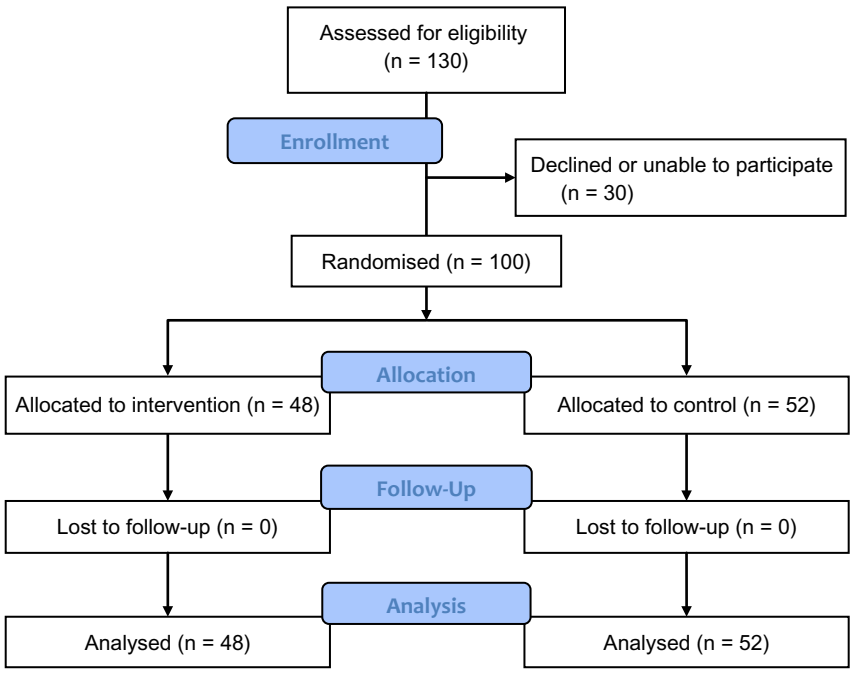

Figure 2. *Consolidated standards of reporting trials (CONSORT) flow diagram.*

the total number of patients with respiratory deterioration and requiring escalation to non-invasive or invasive ventilation was reduced in the HHFNC *versus* standardised oxygen therapy. Electronic medical records were used to obtain presenting problem, triage categories and discharge diagnoses. Primary outcomes between the two groups were compared using χ^2-test. Continuous outcomes and median self-reported comfort scores were compared using Wilcoxon rank sum tests. The estimated sample needed for this study was 100 patients assuming a detected difference in escalation of therapy rates of 30% (85% *vs* 55%) based on previous studies.[10] This was calculated assuming a power of 80% and a two-tailed alpha of 0.05.

Ethics

Ethics approval was obtained from the Human Research Ethics Review Committee RPAH zone (X13-0280 HREC/13//RPAH/367). The trial was registered with the Australian and New Zealand Clinical Trials Registry – ACTRN12613001264774 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365269). Ten AIRVO-2 machines were loaned by Fisher & Paykel for the duration of the study. There was no other external funding or support for the study.

Results

Study population

One hundred and thirty patients were identified by recruiting clinicians of which 30 were unable to consent leaving 100 patients randomised to the study (Fig. 2). Sixty patients were enrolled from tertiary referral ED and 40 from metropolitan district ED. Forty-eight of the patients randomised were allocated to the intervention group and 52 participants to the control group. The mean age was 73.7 years (standard deviation [SD] 14.5) and 56% were men. According to discharge diagnoses from medical records, the primary diagnosis was an exacerbation of chronic obstructive pulmonary disease (COPD) in 45% of cases, respiratory tract infection in 19% of cases, other respiratory diagnoses (pulmonary embolism, asthma, cancer) in 8% of cases and 22% were cardiac related. Baseline characteristics are summarised in Table 2. There were no statistically significant differences in baseline and respiratory state characteristics between the intervention and control study groups.

Outcomes

The intervention group was associated with a higher proportion of patients who had a 20% reduction in RR (66.7% *vs* 38.5% of the controlled group, $P = 0.005$) (Table 3). Only two (4.2%) patients in the intervention group were escalated to more invasive therapy compared with 10 (19.0%) in the control group. The two patients who were escalated in the intervention group were placed on NIV. Of the control group, two patients were escalated to NIV, one was intubated, and seven were escalated to HHFNC. A further two patients in the control group had their oxygen mask settings increased from nasal prong to non-rebreather. In regard to the patients' self-reported dyspnoea scale, 75% from the intervention group reported a reduction in Borg score compared with 55.8% from the control group ($P = 0.044$).

There was no difference between the two groups with respect to disposition from ED or length of stay. There were no adverse events reported in both study groups.

Discussion

The present study demonstrated that the use of HHFNC in ED patients presenting with acute undifferentiated shortness of breath was associated with a reduction in RR, improvement in the patients self-rated dyspnoea (Borg scale), and fewer patients requiring escalation in therapy. There was no difference in length of stay in ED or overall admissions to ICU. Based on these findings, it appears HHFNC might be a more effective intervention in selected patients presenting to ED with shortness of breath compared with traditional nasal prong and oxygen face masks.

The ability to titrate flow and FiO_2 as separate entities appeared to benefit patients who had the potential to develop hypercapnia, where the targeted oxygen saturation range was between 88% and 92%.[13,14] Flow was titrated to patient's work of breathing with the aim to meet or exceed the

TABLE 2. *Comparison of baseline characteristics*

Category	Variable	Control $n = 52$	Intervention $n = 48$
Demographic	Age (mean, SD)	74.5 (14.0)	72.9 (15.1)
	Male (%)	24 (46.2)	20 (41.7)
Mode of arrival (%)	Ambulance	36 (69.2)	29 (60.4)
Triage category (%)			
	1		
	2	37 (71.1)	38 (79.2)
	3	15 (28.9)	10 (20)
	4		
Respiratory	Respiratory rate	33 (6.3)	33 (6.7)
	Oxygen saturation	89 (8.5)	88 (5.4)
	Venous pH	7.39 (0.07)	7.38 (0.07)
Background (%)	Heart failure	14 (26.9)	19 (39.6)
	Chronic obstructive pulmonary disease	37 (71.1)	38 (79.2)
	Home oxygen	10 (19.2)	11 (22.9)
Oxygen therapy on arrival (%)	None	17 (32.7)	17 (35.4)
	Face mask	23 (44.2)	19 (39.6)
	Nasal prong	7 (13.4)	9 (18.8)
	NRB	4 (7.7)	3 (6.2)
Venous pH (mean SD)		7.39 (0.07)	7.38 (0.07)
Venous bicarbonate (mean, SD)		27.0 (5.3)	26.0 (4.1)

NRB, non-rebreather mask.

TABLE 3. *Study outcomes*

Outcome	Control $n = 52$	Intervention $n = 48$	*P*-value
Primary outcomes			
Reduction in respiratory rate >20% from baseline (%)	20 (38.5)	32 (66.7)	0.005
Escalation in ventilation therapy (%)	10 (19.0)	2 (4.2)	0.02
Secondary outcomes			
Reduction in Borg score (%)	29 (55.8)	36 (75)	0.044
Patient comfort score (median IQR)	3 (2–4)	4 (3–4)	0.035
Length of stay in ED (min, median IQR)	302 (231, 434)	265 (180, 485)	0.29
Disposition			
ICU (%)	10 (19)	9 (19)	0.92
Discharged from ED	4 (7.7)	5 (10.4)	0.63

ICU, intensive care unit.

patients' inspiratory flow demand.[15] Higher flows have been demonstrated to flush out nasopharyngeal dead space and provide low levels of positive end expiratory pressure.[8,14] FiO_2 was then titrated according to measured oxygen saturations. The internal blender provided a FiO_2 range from room air 21% to 100% and was accurate because of limited room air entrainment.

HHFNC has provided ED clinicians with another tool in the management of acute dyspnoea particularly in patients with a background of COPD or congestive cardiac failure (CCF) who do not have an indication for immediate NIV or invasive ventilation. HHFNC was generally well tolerated by patients with no adverse events reported in this study or others.[8,10] Anecdotally, patients on HHFNC were able to communicate easily and maintain oral intake because of the absence of a face mask, and this was supported by the slightly improved patient self-reported comfort scores at 1 h. Additionally, once stabilised on HHFNC, these patients were able to be safely managed in an acute ED ward setting rather than a resuscitation bay with 1:1 patient nurse ratios required with NIV.

The results from this study were comparable with those found in previous studies; however, these were in critical care or postoperative clinical settings. Results of particular importance included decreased risk of requiring escalation to NIV or intubation.[10,16–18] Additionally, an improvement in dyspnoea, tachypnoea[6,17,18] and patient comfort[6,7,10,16,18,19] were also comparable. Further research does need to occur in the ED setting to further identify which patients benefit most from the early application of HHFNC and what point escalation should occur.

There was no significant difference between the two groups in regard to ICU admissions. However, this might have been a reflection of different critical care admission policies at the two hospitals – all patients' receiving HHFNC at the metropolitan district hospital were required to be admitted to the high dependency unit because of staffing constraints on the ward. At the tertiary referral hospital, several wards manage patients with HHFNC with flows of up to 45 L and maximum FiO_2 of 45%. A minimum standards guideline for the safe management of patients on HHFNC in the ward environment does need to be developed to support the use of HHFNC in the general ward setting. A post-hoc exploratory analysis of tertiary hospital patients showed a reduction in ICU admission (13% *vs* 4%, $P = 0.37$) although number was small and not statistically significant.

Limitations

The study has several acknowledged limitations, the major one being the

lack of information regarding patients screened and excluded. Given that this was a convenience sample reliant on a pool of registered nurses working in ED, who identified and recruited patients. As a result, it was not possible to determine or compare the subset of number of patients who were excluded for various reasons, and therefore estimate the extent of possible selection bias. The number of patients who required escalation in ventilation therapy in the control group was mostly escalated to HHFNC (seven out of 10 patients) as per study protocol, so it is not possible to determine how many patients were truly prevented from requiring NIV. Objective and subjective measures of respiratory distress in the control group seemed to suggest that at least some of these would have progressed to NIV if HHFNC was limited only to the intervention arm.

The study had a relatively small number of patients; larger studies in the use of HHFNC in ED are warranted. There were a larger proportion of patients with CCF in the intervention group, which was not statistically significant ($P = 0.17$) and might have been due to randomisation. It would have been preferable to have standardised ICU admission criteria across sites; however, it was suspected that the process of roll out to a ward would be too lengthy prior to the study proceeding. Finally, the study was not blinded and therefore subject to observational bias.

Conclusion

The study demonstrated that the use of HHFNC in ED patients presenting with acute undifferentiated shortness of breath was associated with a greater reduction in RR and need for escalation of ventilation requirements compared with standard oxygen therapy. These results suggest that HHFNC should be considered first-line therapy in eligible patients with acute undifferentiated shortness of breath.

Competing interests

None declared.

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