

Pre- and apnoeic high-flow oxygenation for rapid sequence intubation in the emergency department (the Pre-AeRATE trial): A multicentre randomised controlled trial

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ABSTRACT

Introduction: Evidence regarding the efficacy of high-flow nasal cannula (HFNC) oxygenation for preoxygenation and apnoeic oxygenation is conflicting. Our objective is to evaluate whether HFNC oxygenation for preoxygenation and apnoeic oxygenation maintains higher oxygen saturation (SpO₂) during rapid sequence intubation (RSI) in ED patients compared to usual care.

Methods: This was a multicentre, open-label, randomised controlled trial in adult ED patients requiring RSI. Patients were randomly assigned 1:1 to either intervention (HFNC oxygenation at 60L/min) group or control (non-rebreather mask for preoxygenation and nasal prongs of at least 15L/min oxygen flow for apnoeic oxygenation) group. Primary outcome was lowest SpO₂ during the first intubation attempt. Secondary outcomes included incidence of SpO₂ falling below 90% and safe apnoea time.

Results: One hundred and ninety patients were included, with 97 in the intervention and 93 in the control group. Median lowest SpO₂ during the first intubation attempt was 100% in both groups. Incidence of SpO₂ falling below 90% was lower in the intervention group (15.5%) compared to the control group (22.6%) (adjusted relative risk=0.68, 95% confidence interval [CI] 0.37–1.25). Post hoc quantile regression analysis showed that the first quartile of lowest SpO₂ during the first intubation attempt was greater by 5.46% (95% CI 1.48–9.45, *P*=0.007) in the intervention group.

Conclusions: Use of HFNC for preoxygenation and apnoeic oxygenation, when compared to usual care, did not improve lowest SpO₂ during the first intubation attempt but may prolong safe apnoea time.

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INTRODUCTION

Critically ill patients in the emergency department (ED) have shorter safe apnoea times due to physiological distress from decreased cardiac output, increased

shunting and reduced pulmonary reserves.¹ Hypoxia is a commonly encountered adverse event during rapid sequence intubation (RSI)² and is associated with cardiac arrest, neurological injury and death.³ Therefore,

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CLINICAL IMPACT

What is New

- To our knowledge, this is the first randomised controlled trial in the emergency department in Singapore evaluating high-flow nasal cannula (HFNC) oxygenation for preoxygenation and apnoeic oxygenation in patients who required rapid sequence intubation.
- Our study showed that HFNC may prolong safe apnoea time.

Clinical Implications

- Patients with challenging intubation may benefit from the longer safe apnoea time provided by HFNC during preoxygenation and apnoeic oxygenation.

there is significant interest in prolonging safe apnoea time without hypoxia or bag-valve-mask (BVM) ventilation,^{4,5} as the latter may cause aspiration risk in unfasted ED patients, unlike for most patients in intensive care units (ICUs). Existing strategies for preoxygenation include the use of high-flow face mask (HFFM),⁶ such as the non-rebreather mask (NRM) or via well-fitting BVM without additional positive pressure for those with higher degree of respiratory compromise. Apnoeic oxygenation is commonly delivered through application of standard nasal cannula (NC) at 15L/min.⁷⁻¹⁰

Systematic reviews of apnoeic oxygenation in both ICU and ED settings suggest reduction in incidence of hypoxaemia.^{5,11} However, these reviews included heterogenous studies with different apnoeic oxygenation strategies (high-flow nasal cannula [HFNC] versus standard NC at 15L/min) and have differing controls (no intervention, BVM, non-invasive ventilation [NIV] or no control at all).^{5,11} Using HFNC for preoxygenation and apnoeic oxygenation in RSI may offer potential advantages over standard NC. These include better patient tolerance and generation of small amounts of positive end-expiratory pressure.¹² HFNC oxygenation during intubation has been studied in randomised trials,^{13,14} and observational studies in ICUs^{15,16} and EDs.^{17,18} However, its role and effectiveness are still actively debated,¹⁹⁻²¹ with inconsistent evidence regarding its efficacy compared to NIV,^{22,23} HFFM^{23,24} or BVM,¹⁴ and whether it is best utilised in conjunction with NIV.²⁵ Importantly, there has been no randomised

controlled trial in the ED that evaluates the use of HFNC for preoxygenation and apnoeic oxygenation in RSI. Little is known about its efficacy in preventing hypoxia in ED patients during the peri-intubation period.

In our trial, we aimed to evaluate if HFNC use at 60L/min for preoxygenation and apnoeic oxygenation will maintain higher oxygen saturation (SpO₂) for ED patients during RSI, compared to the usual care of preoxygenation with NRM and standard NC with at least 15L/min of oxygen flow for apnoeic oxygenation.

METHODS

Study design and setting

In this Pre- and Apnoeic high flow oxygenation for RAPid sequence intubation in The Emergency department (Pre-AeRATE) study, an open-label, randomised, controlled trial, we enrolled adult patients who required RSI in EDs of the National University Hospital and Ng Teng Fong General Hospital in Singapore. Each ED receives over 110,000 attendances annually and performs 12–20 RSIs monthly. Pre-AeRATE was registered with ClinicalTrials.gov (NCT03396094). Ethics approval for waiver of consent at enrolment and delayed informed consent was obtained from the institutional ethics review board (DSRB reference number 2017/00348) in accordance with the Singapore regulations for clinical trials under emergency situations.²⁶

Subjects were randomised at 1:1 ratio into intervention and control groups, stratified by study site, with variable blocks of 4 and 6 via a web-based randomisation service generated by an independent statistician. Allocation concealment was maintained until completion of randomisation. Blinding of the ED team and patient was not possible due to the intervention. Clinicians in the admitting ICUs were blinded to the study allocation. The full protocol for this study was published elsewhere.²⁷

Selection of participants

Inclusion criteria were patients aged ≥21 years requiring RSI due to any condition. The following were excluded: active “do-not-resuscitate” orders; crash, awake or delayed sequence intubations; requiring non-invasive positive pressure ventilation; cardiac arrest; suspicion or confirmed diagnosis of base of skull fractures or severe facial trauma that precluded placement of NC; pregnant women; and those incarcerated.

Interventions

The intervention group using HFNC received 60L/min of warm and humidified oxygen at 37°C and fraction

of inspired oxygen (FiO_2) of more than 0.90 using the AIRVO 2 Humidifier with Integrated Flow Generator (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) during preoxygenation and apnoeic oxygenation phases. Control group was managed with usual care by preoxygenating using only NRM at flush rate, and then given at least 15L/min of non-humidified and non-heated oxygen from wall supply via NC for apnoeic oxygenation. Flush rate used for NRM preoxygenation reduces leak around the mask margins and is non-inferior to BVM, which is the other recommended modality.²⁸

After ≥ 3 minutes of preoxygenation, induction medications were administered based on treating physician's discretion, and apnoeic oxygenation commenced as per allocation. Intubation was attempted after 30–60 seconds, depending on the paralytic agent. End of intubation was defined as correct placement of endotracheal tube with confirmation using quantitative end-tidal carbon dioxide (ETCO_2) monitoring.

Measurements and outcomes

Vital signs and airway features were assessed prior to preoxygenation. The primary endpoint was lowest SpO_2 during the first intubation attempt, defined as time taken from administration of paralytic agent until quantitative ETCO_2 was detected post-intubation if successful, or until the start of the second attempt if failed. The primary outcome analysis was restricted to the first intubation attempt as clinicians may deviate from initial treatment allocation based on their discretion after the first attempt. SpO_2 was measured using the pulse oximeters, Philips Intellivue MP30 Patient Monitor (Royal Philips, Amsterdam, the Netherlands) and Zoll R Series defibrillator (Zoll Medical Corporation, Chelmsford, US) at 2 different areas in the upper extremities. A research coordinator, nurse or clinician not involved in the intubation recorded the lowest SpO_2 and other variables collected during the attempts. Patients were monitored for peri-intubation adverse events (AEs) such as aspiration, arrhythmia and cardiac arrest during intubation or within 5 minutes after intubation. Main secondary outcomes were incidence of SpO_2 falling below 90% and safe apnoea time during intubation (duration of apnoea where SpO_2 remains $\geq 90\%$ and censored at the time of successful intubation). Other secondary outcomes included number of intubation attempts, time (from induction) to successful intubation, peri-intubation AE, and various post-intubation clinical outcomes.

Sample size calculation

Based on our preliminary data (unpublished) and a previous study,²⁴ we anticipated a standard deviation of 14% in the lowest SpO_2 . Enrolment of 184 patients (92 patients in each control and intervention groups) would provide statistical power of 80% (two-sided α of 0.05) to detect a 6% difference in lowest SpO_2 ,¹⁵ allowing for a 5% dropout.

Data analyses

Analyses of baseline and efficacy data were performed with the intention-to-treat (ITT) population, stratified or adjusted for study site for outcome variables. Supplementary analyses of efficacy data were performed with the per-protocol (PP) population, comprising randomised patients who received FiO_2 of at least 0.70 during preoxygenation and apnoeic oxygenation with no major protocol deviation. This FiO_2 value was chosen as it is the minimum acceptable level to be comparable with that delivered by NRM.²⁹ Frequency and proportion of patients with any peri-intubation AE were summarised in the “as-treated” population, that is, according to actual approaches of preoxygenation and apnoeic oxygenation received.

Since distribution of lowest SpO_2 was highly skewed as observed in similar studies,^{15,24} a stratified Mann-Whitney U test (namely the van Elteren test) was used to compare lowest SpO_2 between treatment groups. Post hoc analysis with quantile regression of lowest SpO_2 was performed with adjustment for covariates, selected backward stepwise into the final adjusted model.³⁰

The Cochran-Mantel-Haenszel test was used to compare risk of SpO_2 below 90% between groups. The common relative risk (RR) was estimated with its 95% confidence interval (CI) by the Mantel-Haenszel method. Safe apnoea time during intubation and time to successful intubation were compared using the stratified log-rank test. The hazard ratios (HR) of SpO_2 falling below 90% and successful intubation were estimated from the Cox proportional hazards model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, US) and $P < 0.05$ indicated statistical significance.

RESULTS

From May 2018 to December 2019, a total of 518 patients were screened and 192 eligible patients were randomised, with 97 assigned to intervention group and 95 to control group. All intervention patients and 93 patients in the control group were included in ITT

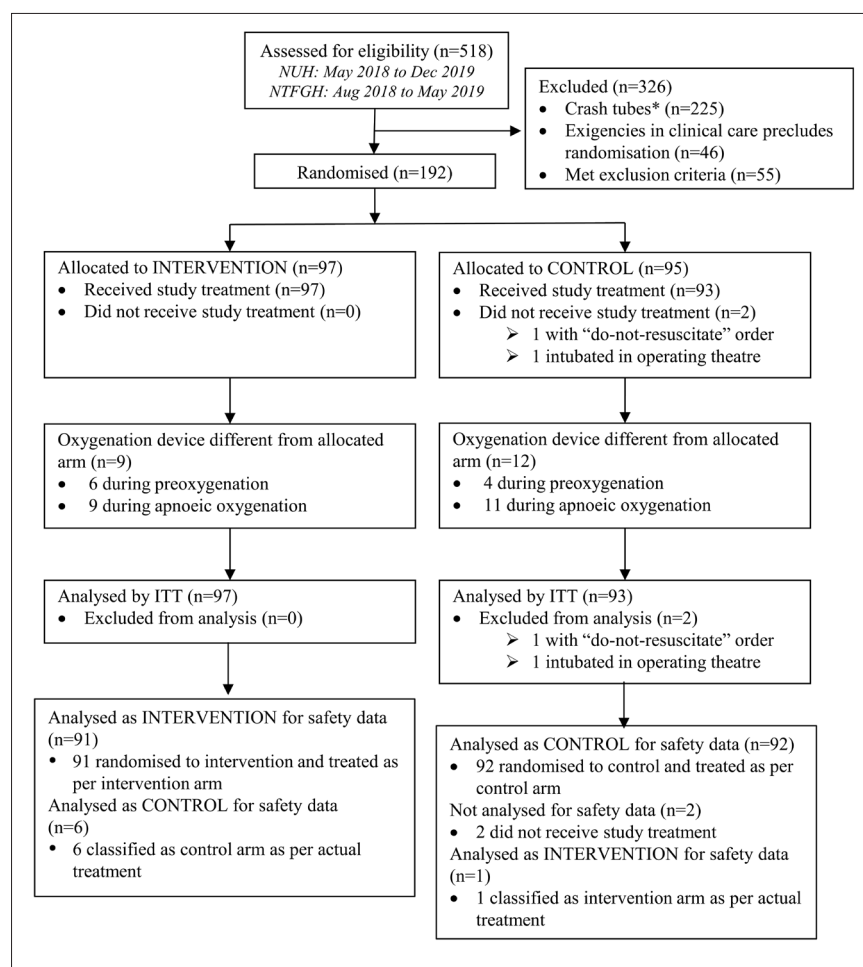


Fig 1. Flowchart illustrating patient enrolment, randomisation and treatment allocation.

ITT: intention-to-treat; NUH: National University Hospital; NTFGH: Ng Teng Fong General Hospital

*Refers to patients who were unconscious and apnoeic

analysis (Fig. 1). In the control group, 2 patients were excluded from data analysis as 1 had a “do-not-resuscitate” order established after randomisation and the other was intubated in the operating room.

Characteristics of study subjects

Overall, there was a predominance of males (124/190, 65.3%) with a mean age of 61.1 years (standard deviation [SD] 15.1) and mean estimated weight of 64.6kg (SD 14.0) (Table 1 and online Supplementary Table 1). The top 3 indications for intubation were non-traumatic intracranial, subarachnoid and subdural haemorrhages (57/190, 30.0%); shock states (28/190, 14.7%); and seizures (23/190, 12.1%).

Most patients were assessed to have no potential airway difficulty (121/190, 63.7%). A great proportion (176/190, 92.6%) were intubated using

the C-MAC (Karl Storz, Tuttlingen, Germany) video laryngoscope; 20 patients (10.6%) had Grade 3 or 4 laryngeal view by the Cormack-Lehane classification. Most received NRM before randomisation (intervention 52/97 [53.6%] and control 44/93 [47.8%]; see online Supplementary Table 2) as part of prehospital care. Full data relating to the study procedure and treatment are summarised in the online Supplementary Tables 2 and 3.

Outcomes

Lowest SpO₂ was maintained at 100% during the first intubation attempt in more than half of the patients in both groups. There was no statistical difference in the lowest SpO₂ recorded during the first intubation attempt between the intervention (median SpO₂ 100%, interquartile range [IQR] 96.0–100) and control groups (median SpO₂ 100%, IQR 91.0–100)

Table 1. Demographics, baseline characteristics and airway features

	Intervention (n=97)	Control (n=93)	Total (N=190)
Demographics and baseline characteristics			
Age, mean (SD), years	60.4 (15.4)	61.9 (14.7)	61.1 (15.1)
Sex, male, no. (%)	59 (60.8)	65 (69.9)	124 (65.3)
Body mass index, mean (SD), kg/m ²	23.4 (4.0)	24.5 (4.7)	24.0 (4.4)
Indication for intubation, no. (%)			
Asthma/COPD	2 (2.1)	1 (1.1)	3 (1.6)
Fluid overload, cardiac/renal	4 (4.1)	5 (5.4)	9 (4.7)
Gastrointestinal bleed	6 (6.2)	6 (6.5)	12 (6.3)
ICH/SAH/SDH (non-traumatic)	34 (35.1)	23 (24.7)	57 (30.0)
Pneumonia	10 (10.3)	7 (7.5)	17 (8.9)
Shock states			
Cardiogenic	1 (1.0)	6 (6.5)	7 (3.7)
Septic	6 (6.2)	13 (14.0)	19 (10.0)
Hypovolaemic	0 (0)	2 (2.2)	2 (1.1)
Seizures	11 (11.3)	12 (12.9)	23 (12.1)
Trauma	7 (7.2)	5 (5.4)	12 (6.3)
Others	16 (16.5)	13 (14.0)	29 (15.3)
Glasgow Coma Scale, median (Q1, Q3)	7 (6, 14)	10 (6, 14)	8 (6, 14)
Vasopressor use, no. (%)	7 (7.2)	13 (14.0)	20 (10.5)
Abnormal chest X-ray findings, no. (%)	41 (42.3)	42 (46.2)	83 (44.1)
Airway features			
Potential airway difficulty, no. (%)			
Reduced neck mobility or in cervical collar	11 (11.3)	11 (11.8)	22 (11.6)
Airway obstruction	2 (2.1)	1 (1.1)	3 (1.6)
Facial trauma	2 (2.1)	1 (1.1)	3 (1.6)
Blood or vomitus in airway	17 (17.5)	13 (14.0)	30 (15.8)
Others	11 (11.3)	12 (12.9)	23 (12.1)
None	61 (62.9)	60 (64.5)	121 (63.7)
Mallampati score, no. (%)			
Class 1	9 (9.3)	6 (6.5)	15 (7.9)
Class 2	14 (14.4)	14 (15.1)	28 (14.7)
Class 3	11 (11.3)	16 (17.2)	27 (14.2)
Class 4	6 (6.2)	6 (6.5)	12 (6.3)
Not assessed	57 (58.8)	51 (54.8)	108 (56.8)

Table 1. Demographics, baseline characteristics and airway features (Cont'd)

	Intervention (n=97)	Control (n=93)	Total (N=190)
Mouth opening, no. (%)			
Normal (≥ 3 fingerbreadths)	45 (46.4)	36 (38.7)	81 (42.6)
Reduced (1 or 2 fingerbreadths)	25 (25.8)	32 (34.4)	57 (30.0)
Not assessed	27 (27.8)	25 (26.9)	52 (27.4)
Thyromental distance (fingerbreadth), no. (%)			
1	3 (3.1)	1 (1.1)	4 (2.1)
2	33 (34.0)	37 (39.8)	70 (36.8)
3	38 (39.2)	41 (44.1)	79 (41.6)
≥ 4	2 (2.1)	2 (2.2)	4 (2.1)
Not assessed	21 (21.6)	12 (12.9)	33 (17.4)
Cormack-Lehane classification of laryngeal view, no. (%)			
Grade 1	50 (51.5)	52 (56.5)	102 (54.0)
Grade 2	36 (37.1)	31 (33.7)	67 (35.4)
Grade 3	8 (8.2)	9 (9.8)	17 (9.0)
Grade 4	3 (3.1)	0 (0)	3 (1.6)
Type of laryngoscope, no. (%)			
Direct	9 (9.3)	5 (5.4)	14 (7.4)
Video	88 (90.7)	88 (94.6)	176 (92.6)

COPD: chronic obstructive pulmonary disease; ICH: intracranial haemorrhage; Q1: 25th percentile; Q3: 75th percentile; SAH: subarachnoid haemorrhage; SDH: subdural haemorrhage

Additional baseline demographics are presented in online Supplementary Table 1.

(Table 2 and Fig. 2). Comparison of lowest SpO₂ between the 2 groups using the stratified Mann-Whitney U test provided *P* values of 0.138 and 0.061 in ITT and PP populations, respectively (Table 2). A post hoc quantile regression analysis of the first quartile of lowest SpO₂ (adjusted for indication for intubation, potential airway difficulty and baseline SpO₂) estimated a difference of 5.5% (95% CI 1.5–9.5, *P*=0.007) in first quartile between the 2 groups (online Supplementary Table 4). Outcomes were comparable between groups with respect to number of intubation attempts and time to successful intubation. Most patients were successfully intubated at first attempt (intervention group 80/97 [82.5%] versus control group 78/93 [83.9%]). Median time from induction to successful intubation was 3.0 minutes in the intervention group and 3.5 minutes in the control group (Table 2). Treatment in intervention group reduced the risk of SpO₂ falling below 90% by at least 30% during the first intubation attempt and any attempt (adjusted RRs

0.55, *P*=0.084; 0.52, *P*=0.057 in first and any attempt in the PP population; and adjusted RRs 0.68, *P*=0.213; 0.65, *P*=0.156 in first and any attempt in the ITT population). Median safe apnoea time was prolonged by 3.0 minutes in the intervention group (10 minutes) compared to the control group (7 minutes), with HR of SpO₂ falling below 90% = 0.57 (95% CI 0.28–1.12, *P*=0.104).

Incidences of ventilator-associated pneumonia and aspiration pneumonia were comparable between both groups (22.6% vs 22.7%). The treatment in the intervention group did not affect other clinical outcomes (Table 3). Seventeen (18.5%) patients in the intervention group and 13 (13.3%) patients in the control group experienced peri-intubation AE (Table 3).

DISCUSSION

In our cohort, SpO₂ was maintained at 100% in more than 50% of patients in both groups. Use of HFNC compared with routine care did not show any statistically

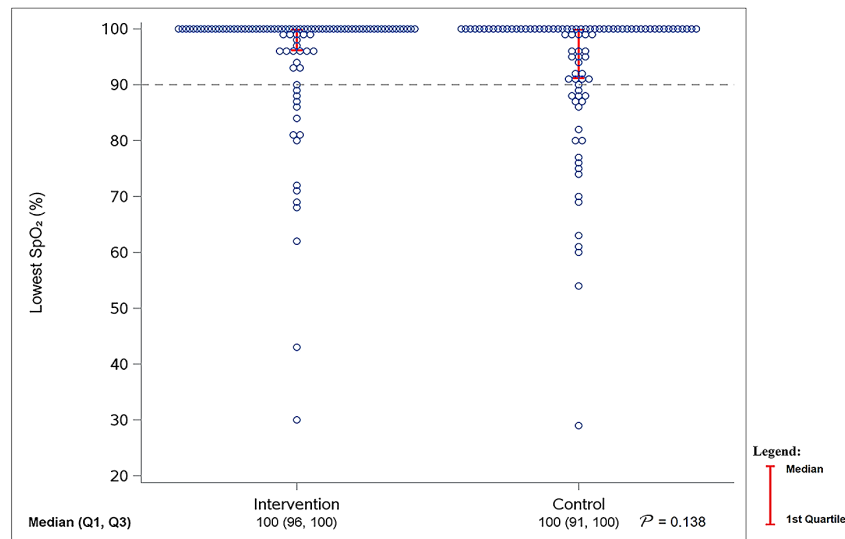


Fig. 2. Lowest SpO₂ during first intubation attempt.

SpO₂: oxygen saturation; Q1: 25th percentile; Q3: 75th percentile

significant difference in oxygenation during the first and subsequent intubation attempts. These observations could be due to the result of better physiological reserves in our cohort, which largely comprised patients with neurological emergencies. However, in our post hoc analysis, patients having lowest SpO₂ of below 95% with usual care were expected to have their lowest SpO₂ improved by an average of 5% if they were managed with HFNC ($P=0.032$ from Mann-Whitney U test in this subgroup). This is clinically important as the oxygen dissociation curve has a steep gradient below 90% and patients can reach critical hypoxic state in a span of seconds.³¹ After adjustment for significant covariates using quantile regression analysis, the first quartile of lowest SpO₂ achieved during the first intubation attempt was greater by 5.5% (95% CI 1.5–9.5, $P=0.007$) in the intervention group compared to the control group. This is consistent with a recent network meta-analysis, which showed that HFNC or NIV was better than conventional oxygen therapy for preoxygenation in ICU, at least in terms of lowest SpO₂ achieved.³² Our study results add to the evidence by examining peri-intubation HFNC in ED patients.

An acceptable alternative strategy to optimise SpO₂ for intubation is through positive pressure ventilation using NIV.⁴ Although NIV may be superior to conventional oxygenation therapy in preoxygenation, its use may be limited if patients are obtunded, have emesis or are unable to tolerate face masks.^{22,33} Unlike NIV, HFNC allows apnoeic oxygenation during intubation without additional maneuvers. Studies comparing HFNC versus

NIV have yielded inconsistent results. In the largest study to-date ($n=313$), neither modality reduced risk of severe hypoxia during intubation,³⁴ though there seems to be potential synergistic benefit in combining NIV with HFNC.²⁵ Nevertheless, combining the use of both NIV and HFNC has its problems of inadequate mask seal due to obstruction from the HFNC nasal cannula, as well as increase in procedural complexity and healthcare costs due to using 2 oxygen delivery devices. This may not be adequate given current dearth in evidence for this oxygenation method.

Our study showed that HFNC was safe compared to our usual care. The intervention patients had lower median pre-intubation Glasgow Coma Scale (7 [IQR 6–14]) compared to controls (10 [IQR 6–14]). However, we did not observe significant increase in aspiration risk and other adverse events. The safety of HFNC use in RSI was replicated in other existing literature.¹⁴ Pending availability of more evidence, HFNC can be considered as a useful alternative in selected patients with contraindications to NIV, given its safety profile and better tolerance.

Apart from optimising preoxygenation, apnoeic oxygenation is a strategy that can prevent peri-intubation desaturation. Physiologically during apnoea, the much higher solubility of carbon dioxide in blood compared to oxygen allows oxygen to move more readily from alveoli into the bloodstream. This creates a sub-atmospheric alveolar pressure, allowing passive flow of oxygen from the pharynx to alveoli. Despite this rationale, previous randomised controlled trials in the ED and ICU did not demonstrate significant benefit

Table 2. Study outcomes at intubation

	Intention-to-treat analysis		Per-protocol analysis	
Characteristic	Intervention (n=97)	Control (n=93)	Intervention (n=86)	Control (n=91)
Lowest SpO ₂ during first attempt, %				
Median (Q1, Q3)	100.0 (96.0, 100.0)	100.0 (91.0, 100.0)	100.0 (99.0, 100.0)	100.0 (91.0, 100.0)
Median diff (95% CI) [<i>P</i> value]	0 (0–4.0) [0.138 ^a]		0 (0–1.0) [0.061 ^a]	
Lowest SpO ₂ during all intubation attempts, %				
Median (Q1, Q3)	100.0 (96.0, 100.0)	100.0 (90.5, 100.0)	100.0 (99.0, 100.0)	100.0 (91.0, 100.0)
Median diff (95% CI) [<i>P</i> value]	0 (0–4.0) [0.072 ^a]		0 (0–2.5) [0.029 ^a]	
Change in SpO ₂ from baseline to end of preoxygenation, %				
Median (Q1, Q3)	0.5 (0, 3.5)	1.0 (0, 5.0)	0 (0, 3.0)	1.0 (0, 5.0)
Median diff (95% CI) [<i>P</i> value]	-0.5 (-2.0–1.0) [0.633 ^a]		-1.0 (-2.0–1.0) [0.500 ^a]	
Change in SpO ₂ from end of preoxygenation to the lowest SpO ₂ during all intubation attempts, %				
Median (Q1, Q3)	0 (-2.0, 0)	0 (-8.0, 0)	0 (-1.0, 0)	0 (-6.0, 0)
Median diff (95% CI) [<i>P</i> value]	0 (0–1.0) [0.094 ^a]		0 (0–0.5) [0.029 ^a]	
Number of intubation attempts, no. (%)				
1	80 (82.5)	78 (83.9)	72 (83.7)	76 (83.5)
2	14 (14.4)	9 (9.7)	11 (12.8)	9 (9.9)
≥3	3 (3.1)	6 (6.5)	3 (3.5)	6 (6.6)
<i>P</i> value	0.439 ^b		0.648 ^b	
Incidence of SpO ₂ <90%, no. (%)				
At first attempt	15 (15.5)	21 (22.6)	10 (11.6)	19 (20.9)
Adj RR (95% CI) [<i>P</i> value]	0.68 (0.37–1.25) [0.213]		0.55 (0.27–1.10) [0.084]	
At any attempt	15 (15.5)	22 (23.7)	10 (11.6)	20 (22.0)
Adj RR (95% CI) [<i>P</i> value]	0.65 (0.36–1.19) [0.156]		0.52 (0.26–1.04) [0.057]	
Safe apnoea time, min				
Median (95% CI)	10.0 (8.0–U)	7.0 (5.5–12.0)	11.0 (8.0–U)	7.0 (6.0–12.0)
HR (95% CI)	0.57 (0.28–1.12)		0.48 (0.22–1.05)	
<i>P</i> value	0.082 ^c	0.104 ^d	0.050 ^c	0.066 ^d
Time to successful intubation, min				
Median (95% CI)	3.0 (3.0–4.0)	3.5 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)
HR (95% CI)	0.98 (0.73–1.30)		1.00 (0.74–1.34)	
<i>P</i> value	0.842 ^c	0.866 ^d	0.940 ^c	0.983 ^d

Adj RR: adjusted relative risk; CI: confidence interval; HR: hazard ratio; Median diff: median difference; U: unable to be estimated; Q1: 25th percentile; Q3: 75th percentile; SD: standard deviation; SpO₂: oxygen saturation

^a *P* value from van Elteren test

^b *P* value from chi-square test or Fisher's Exact test if more appropriate

^c *P* value from stratified log-rank test

^d *P* value from chi-square test of hazard ratio

Table 3. Clinical outcomes and adverse events

Characteristic	Intervention	Control	Effect size (95% CI)	P value
Clinical outcomes (intention-to-treat population)				
	n=97	n=93	Adj RR (95% CI)	
Ventilator associated pneumonia and aspiration pneumonia, no. (%)	21 (22.6)	20 (22.7)	0.99 (0.58–1.70)	0.984 ^a
Acute respiratory distress syndrome, no. (%)	3 (3.2)	5 (5.7)	0.58 (0.14–2.32)	0.431 ^a
Mortality in ICU, no. (%)	14 (15.4)	11 (13.3)	1.17 (0.56–2.42)	0.682 ^a
Mortality on discharge, no. (%)	24 (25.8)	21 (23.9)	1.08 (0.65–1.79)	0.770 ^a
Died in ED	1 (1.1)	4 (4.5)		
Died on discharge	23 (24.7)	17 (19.3)		
Number of ventilated days			Median diff (95% CI)	0.381 ^b
Median (Q1, Q3)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	0 (-1.0, 1.0)	
Length of stay in ICU, days				
Median (Q1, Q3)	4.0 (2.0, 7.0)	3.0 (2.0, 8.0)	1.0 (-1.0, 2.0)	0.615 ^b
Highest SOFA score				
Median (Q1, Q3)	7.0 (5.0, 10.0)	8.0 (6.0, 11.0)	-1.0 (-2.0, 0)	0.112 ^b
Adverse events (as-treated population)				
	n=92	n=98	Adj RR (95% CI)	
Patients with any peri-intubation adverse events	17 (18.5)	13 (13.3)	1.39 (0.72, 2.71)	0.426 ^b
Type of peri-intubation adverse events ^d				
Aspiration	1 (1.1)	0 (0)	NA	0.484 ^c
Bradycardia	2 (2.2)	3 (3.1)	0.71 (0.12, 4.15)	1.000 ^c
Cardiac arrest	3 (3.3)	1 (1.0)	3.20 (0.34, 30.17)	0.356 ^c
Cardiac arrhythmia	0 (0)	3 (3.1)	NA	0.247 ^c
Hypertension	4 (4.3)	5 (5.1)	0.85 (0.24, 3.08)	1.000 ^c
Hypotension	4 (4.3)	3 (3.1)	1.42 (0.33, 6.18)	0.714 ^c
Oropharynx or dental trauma	0 (0)	2 (2.0)	NA	0.498 ^c
Regurgitation	0 (0)	0 (0)	NA	1.000 ^c
Tachycardia	4 (4.3)	2 (2.0)	2.13 (0.40, 11.36)	0.433 ^c
Others	0 (0)	0 (0)	NA	1.000 ^c
Action taken to study treatment				
Continued with allocated group	15 (16.3)	13 (13.3)		
Changed to other oxygenation techniques	1 (1.1)	0 (0)		
Adverse events caused patient to be discontinued from study	0	0		

Adj RR: adjusted relative risk; CI: confidence interval; ED: emergency department; ICU: intensive care unit; median diff: median difference; NA: not available; Q1: 25th percentile; Q3: 75th percentile; SOFA: Sequential Organ Failure Assessment

^a P value from van Elteren test

^b P value from Cochran-Mantel-Haenszel test

^c For number of events <10, Fisher's Exact test was used instead of Cochran-Mantel-Haenszel test

^d Peri-intubation adverse events (occurring during or within 5 minutes after intubation) were defined as: bradycardia (defined as heart rate <60 beats per minute or decrease by >20%); tachycardia (defined as heart rate >100 beats per minute or increase by >20%); hypotension (defined as systolic blood pressure <90mmHg or decrease by >20%); hypertension (defined as systolic blood pressure >140mmHg or increase by >20%)

in improving lowest SpO₂ during intubation.^{8,35} These negative findings could be a result of study procedural limitations. In both studies, oxygen flow at 15L/min was delivered through standard NC that are not designed for such flows. Additionally, a flow of at least 30L/min is necessary before positive airway pressures could be generated.³⁶ By using an HFNC device that can deliver up to 60L/min of high-flow oxygenation and that is specifically designed for this purpose, we were able to overcome these limitations. We showed a lower risk of SpO₂ falling below 90% in the intervention group at the first and any attempt, and safe apnoea time was prolonged by at least 3 minutes (Table 1). Despite lack of statistical significance, this could be clinically significant for 2 reasons. First, an SpO₂ of 90% represents the beginning of the steep down-sloping gradient of the oxygen dissociation curve, whereby small changes in the arterial partial pressure of oxygen (PaO₂) result in large changes in haemoglobin oxygen binding capacity.³⁷ Second, an ill average-sized adult could reach an SpO₂ of less than 60% in under 2 minutes once SpO₂ drops to 90%.³¹ Hence, prolonging safe apnoea time is of utmost importance.

Pre-AeRATE has several strengths. First, this is the only randomised controlled trial to-date evaluating HFNC use for RSI in ED, in Singapore. Second, to our knowledge, this is also the largest trial (190 patients analysed) comparing HFNC with standard oxygen therapy during the peri-intubation period in any clinical setting, in Singapore.^{13,14,24,38,39} Third, we conducted a post hoc analysis employing a quantile regression analysis as an endpoint due to the skewed distribution in such studies and in our cohort (Fig. 2), where a minority would experience much greater desaturation.⁴⁰ This allowed us to generate a hypothesis on the usefulness of HFNC on these patients in extremis. Despite similar decrease in median SpO₂ between the intervention and control arms, safe apnoeic time was noted to be prolonged by HFNC use. Fourth, this pragmatic trial reflects real-world conditions, and shows the plausibility of using HFNC for a time-sensitive procedure in ED and in patients with high aspiration risk, such as trauma with bloody airways and depressed consciousness.

Limitations

This trial has its limitations. First, the time-sensitive nature of RSI precluded measurements of PaO₂ in our protocol, thereby rendering stratification of severity based on hypoxaemia impossible. SpO₂ was used as an endpoint instead, as it is a ubiquitous non-invasive clinical parameter that allows better external validity. Second, it was impracticable to blind patients and

ED clinical staff due to the nature of the intervention. However, objective measurements of SpO₂ by 2 separate devices and blinding of the ICU teams to study allocation made biasing of results unlikely. Third, consecutive recruitment was not possible due to clinicians focusing on resuscitation in the fast-paced ED environment.

Fourth, although we included patients requiring RSI due to any indication, our eventual cohort comprised 42.1% of neurological conditions (intracranial haemorrhage and seizures) and may under-represent those with predominantly cardiorespiratory compromise, who could provide greater physiological insight. As this trial was designed to be pragmatic, we did not specify strict inclusion criteria due to indications for intubation. The observation of more than 50% of patients in each treatment group maintaining SpO₂ at 100% during the first intubation attempt may be attributed to better cardiorespiratory reserves and low risk of desaturation in patients with predominant neurological conditions. By performing post hoc regression analysis of the first quartile of lowest SpO₂, we were able to evaluate the treatment effect on patients in physiological extremis who had higher desaturation risk (compared to the general study population). Although the intervention group comprised a slightly higher proportion of neurological conditions by chance, this difference was not statistically significant. Lastly, given our primary endpoint was to evaluate the lowest SpO₂ achieved, the study was not powered to make meaningful conclusions regarding patient-oriented outcomes such as mortality or length of ICU stay. Future studies should focus on such endpoints, other long-term outcomes and evaluate the cost-effectiveness of using HFNC during the peri-intubation period.

CONCLUSION

We found that HFNC use for preoxygenation and apnoeic oxygenation, when compared to usual care, did not show improvement in median lowest SpO₂ achieved during the first intubation attempt. However, such HFNC use may prolong safe apnoea time. Our study showed that patients without neurological indications for intubation were likely to desaturate faster, or have a more challenging intubation, and may benefit from the longer apnoea time that HFNC provides.

Disclosure

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Trial registration

ClinicalTrials.gov (NCT03396094). Registered on 10 January 2018.

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