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ORIGINAL ARTICLE

High flow humidified nasal oxygen to prevent desaturation during Endobronchial Ultrasound procedure: a randomised controlled trial

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Summary

Traditional conscious sedation for endobronchial ultrasound procedures place patients at risk of desaturation, and high-flow nasal oxygen may reduce the risk.

We designed a parallel group randomised controlled trial of high flow nasal oxygen at a flow rate of 30-70 $l.min^{-1}$ via nasal cannulae, compared to standard oxygen therapy at 10 $l.min^{-1}$ via a bite block in adults planned for conscious sedation for endobronchial ultrasound. The primary outcome was the proportion of patients experiencing desaturation (defined as a SpO_2 <90%). Secondary outcomes included oxygen saturation after pre-oxygenation, lowest oxygen saturation during procedure, number of hypoxic episodes, duration of hypoxia, end-procedure end-tidal CO_2, satisfaction scores and complications.

Thirty participants were allocated to each group. Baseline patient characteristics, procedure time and anaesthetic agents used were similar between the groups. Desaturation occurred in four of 30 patients allocated to the high-flow nasal oxygen group, compared to 10 of 30 allocated to the standard oxygenation group, a non-significant difference (p=0.07) with intention-to-treat analysis. The difference was significant (p =0.047) when using a per-protocol analysis. Oxygen saturation after pre-oxygenation and the lowest oxygen saturation during procedure were significantly higher in the high flow nasal oxygen group compared to the standard oxygenation group; median (IQR [range] 100 (99-100 [93-100]) vs. 98 (97-99 [94-100]), p=0.0001 and (97.5 (94-99 [77-100]) vs. 92 (88-95 [79-98]), p=0.0000 respectively. There were no differences for other secondary outcomes.

While high-flow nasal oxygen may prevent desaturation due to some causes, it does not protect against hypoventilation in all circumstances.

Introduction

Endobronchial Ultrasound (EBUS) is a commonly used diagnostic procedure performed in am endoscopy suite to obtain tissue samples for pathological analysis [1]. Patients are usually suspected of having lung cancer [1], with other common indications for EBUS including suspected tuberculosis [2], lymphoma [3] or sarcoidosis. Patients frequently have co-existing lung disease [4].

Sedation for EBUS should make the procedure tolerable for the patient, reduce or eliminate coughing to maximise procedural safety, whilst avoiding hypoxaemia (which may be life-threatening). A combination of sedative agents and opioids are commonly used, though previous trials reported this combination led to desaturation in up to 45% of patients [5], either due to airway obstruction or hypoventilation by direct central suppression of ventilation.

The procedure is routinely performed using conscious sedation. Airway management is difficult during EBUS; the airway is shared between the anaesthetist and the operator [6], and there is no efficient technique to ventilate the patient whilst the procedure is in progress. If desaturation (defined as a SpO_2 of <90%) occurs, the procedure is stopped, the patient ventilated, and the procedure restarted. Despite these disadvantages, conscious sedation is preferred over general anaesthesia due to its greater cost-effectiveness [7] and good patient and operator satisfaction [8].

The OptiFlow THRIVE device (Fisher and Paykel Healthcare, Panmure, Auckland, New Zealand) is a high-flow, trans-nasal oxygen delivery device that may extend the time until desaturation occurs, and is well tolerated by patients [9-11]. It delivers a flow of 10-70 $l.min^{-1}$ of humidified, warmed 100% oxygen via nasal cannula. The device has been used extensively in Intensive Care in both adults and children for many years in patients with hypoxaemic respiratory failure [12].

The current method of conscious sedation for EBUS leaves patients vulnerable to desaturation. Addition of high flow nasal oxygen (HFNO) may reduce the incidence of desaturation in these patients, and may reduce the frequency with which procedures are interrupted by the need to ventilate the patients.

This study aimed to evaluate the role of HFNO during sedation for EBUS. The study hypothesised that in adults undergoing EBUS, the use of HFNO would result in lower rates of desaturation than standard oxygen delivery methods.

Methods

Ethical approval was given the by the Melbourne Health Human Research Ethics Committee (HREC Reference Number: HREC/16/MH/312, Melbourne Health Site Reference Number: 2016.168). All participants provided written informed consent before recruitment to study. The trial was registered with the Australia and New Zealand Clinical Trials Registry with the number ACTRN12616001691437 and with the Universal Trial Number U1111-1183-6921.

The study was a prospective randomised controlled trial, comparing high flow HFNO to standard oxygenation during EBUS. It was conducted in a single centre, the Royal Melbourne Hospital in Melbourne, Victoria, Australia, and ran from 14/2/17 until 23/5/17. All procedures were carried out in the endoscopy suite. Follow-up for all patients concluded on the day of recruitment. The trial was stopped when the target number of participants was recruited.

Inclusion criteria were: age ≥18 years; able to give informed consent; sedation planned; English speaking (due to lack of available interpreter support). In line with the manufacturer's instructions and ethical requirements, exclusion criteria were: age <18 years; unable to consent; intubated or requiring intubation for procedure; pregnant; active nasal bleeding or base of skull fracture.

The OptiFlow THRIVE at a flow rate of 30-70 $l.min^{-1}$ with 100% oxygen was used in the HFNO group. The standard oxygenation group received oxygen at 10 $l.min^{-1}$ via a bite block. EBUS was conducted using an Olympus bronchoscope, both radial and linear types, introduced through a sheath manufactured by Olympus (Notting Hill, Victoria, Australia).

All patients presenting for EBUS during the study period were screened by one of the investigators (FN). Computer-generated randomisation was used in blocks of 10. A total of 60 participants were recruited, of which 30 were allocated to each group in a parallel one to one ratio. Allocations were concealed by putting the allocation in numbered and sealed envelopes prior to recruitment. Participants, treating anaesthetist and the investigator responsible for recruitment were not aware of the randomisation group prior to consent. The allocation was revealed only after the patient was consented to participate in the study. Due to the different appearance of the oxygenation devices, it was not possible to blind the participants, data collector or anaesthetists to group allocation while the procedure was conducted.

After written informed consent, patients were assigned, according to the computer-generated randomisation result, to have their oxygen delivered via HFNO or standard oxygenation. The patient's baseline characteristics, including age, sex, height and weight, American Society of Anesthesiologists (ASA) Physical Status, underlying respiratory illnesses and baseline oxygen saturation (SpO_2) without oxygen were recorded pre-operatively. Procedural data, including type and duration of procedure, anaesthetic agents used, minimum and maximum oxygen delivery rates were also collected. Patients were sedated in an area with appropriate monitoring, resuscitation equipment and assistance in accordance with the Australian and New Zealand College of Anaesthetists' guidelines. Oxygen was administered to the patient via the allocated device immediately after arrival in the bronchoscopy room. The HFNO humidifer was turned on in the bronchoscopy room for at least 10 minutes before arrival of the patient to allow the humidifier to warm.

In the HFNO group, patients were given 100% oxygen at 30 $l.min^{-1}$. In the standard oxygenation group, patients were put on oxygen at 10 $l.min^{-1}$. These flow rates continued until sedation was administered. SpO_2 after pre-oxygenation was recorded before sedation was given. The treating anaesthetist then gave sedative agents, such as midazolam, opioids and/or propofol, at his/her own discretion, and titrated the sedation depth to the target of "Modified Observer's Assessment of Alertness/Sedation Scale" (MOAA/S) = 4. A bite block was used in all patients to protect the bronchoscope.

In the HFNO group, the oxygen delivering rate was increased to 50 $l.min^{-1}$ immediately after sedative agents were given, and was maintained at 50 $l.min^{-1}$ during the procedure. The flow rate could be increased up to 70 $l.min^{-1}$ if necessary or decreased to 30 $l.min^{-1}$ if the patient did not tolerate the higher flow rate. In the standard oxygenation group, the oxygen flow rate, delivered via the bite block remained at 10 $l.min^{-1}$ during the procedure, but could be increased up to 15 $l.min^{-1}$ if necessary.

At any stage of the study, the anaesthetists could manage the airway in any way they deemed appropriate, if they were concerned or they perceived that it was in the best interest of the patient. This included changing to the alternative oxygen delivery strategy.

Either radial probe EBUS investigation of peripheral pulmonary lesions, or EBUS-guided transbronchial needle aspiration (EBUS-TBNA) was performed by the

respiratory unit physician and/or fellow, who applied topical lignocaine 2% to the patient's naso- and oropharynx as per routine practice at the beginning of the procedure, followed by further topicalisation to the vocal cords and trachea.

An independent observer was present during the procedure to collect all the relevant data which was transcribed from the case report form. The observer did not participate in anaesthetic care. After the procedure was complete, a five-point Likert scale satisfaction score (very satisfied / satisfied / neither satisfied nor dissatisfied / dissatisfied / very dissatisfied) was obtained from the operator, the anaesthetist and the patient.

The primary outcome was the proportion of patients experiencing desaturation below 90% during the procedure. Secondary outcomes included: oxygen saturation (SpO_2) after pre-oxygenation before sedation is given; lowest SpO_2 during the procedure; number of hypoxic episodes (SpO_2 below 90%) during the procedure; duration of hypoxia during the procedure; end-procedure end-tidal CO_2 (which was measured from the distal trachea using a mixing cannula inserted into the working channel of the bronchoscope); patient satisfaction score; operator satisfaction score; anaesthetist satisfaction score; any complications, including number of interruptions to procedure to allow anaesthetic management, arrhythmia, myocardial ischaemia and cardiac arrest.

A sample size calculation was performed, assuming a 48% desaturation rate in the standard oxygen therapy group [13] compared to a 15% rate in the HFNO group. It was calculated that a total of 30 participants in each group would provide 80% power at a significance level of 0.5.

Patient baseline characteristics, procedural data and complications were presented descriptively. Chi-squared test was used to examine the proportion of patients experiencing desaturation and the number of hypoxic episodes. The Mann Whitney U-test was used to examine the SpO_2 after pre-oxygenation, lowest SpO_2 during procedure, duration of hypoxia during procedure, end-procedure end-tidal CO_2 level and satisfaction scores. A p value < 0.05 was considered statistically significant. Data were analysed as intention to treat. Statistical analysis was performed using Stata 13.0 (Statacorp, College Station, Texas, USA).

Results

A total of 60 patients were recruited, and 30 were allocated to each group. Baseline characteristics and procedural data of the two groups are presented in Table 1.

Cross-over (from the standard oxygenation group to the HFNO group) occurred twice. One patient was allocated to the standard oxygenation group but was deemed unsuitable for this by the treating anaesthetist, who used HFNO instead for that patient from the beginning of the procedure. A second patient in the standard oxygenation group desaturated midway through the procedure, and the treating anaesthetist elected to change to HFNO. Both patients remained in their allocated treatment groups for analysis. The CONSORT diagram for recruitment is presented in Fig 1.

The primary outcome of desaturation below SpO_2 90% occurred in four of 30 of the patients in the high flow nasal oxygen group, compared to 10 of 30 patients in the standard oxygenation group when analysed using an intention to treat approach. This difference did not reach the threshold of statistical significance (p=0.07). These results represent an absolute risk reduction of 21%, a relative risk reduction of 40% and a number needed to treat of 4.7. This did reach statistical significance when analysed using a per-protocol approach (p=0.048), with the primary outcome occurring in four of 31 patients in the HFNO group compared to 10 of 29 patients in the standard oxygenation group. The per-protocol analysis involved moving the patients allocated to the standard oxygenation group (but deemed unsuitable by the treating anaesthetist) to the HFNO group.

The SpO_2 following pre-oxygenation was significantly higher in the HFNO group compared to the standard oxygenation group (Table 2). The median lowest SpO2 observed during the procedure in the HFNO group was significantly higher than in the standard oxygenation group. There were no differences in other secondary outcomes.

Three patients required interruption of the procedure for airway management (two in standard oxygenation group and one in HFNO group). Apnoea occurred in the HFNO group in two patients, compared to none in the standard oxygenation group. No patient in either group had any other complications, and none required transfer to a higher level of care.

A single exploratory analysis was conducted after conclusion of the trial to examine the link between hypercapnia (defined as an $EtCO_2$ greater than 45mmHg)

and desaturation. A threshold of significance was set at $p < 0.05$. In the HFNO group (in which 23 patients had an available $EtCO_2$ result) hypercapnia (but not desaturation) was seen in seven patients, while desaturation (but not hypercapnia) was not observed. Both hypercapnia and desaturation were seen in three patients in this group, while neither hypercapnia nor desaturation were seen in 13. These results did reach the threshold of significance ($p = 0.03$). In the standard oxygenation group (in which 26 patients had an available $EtCO_2$ result) hypercapnia (but not desaturation) was seen in four of 26 patients, while desaturation (but not hypercapnia) was also seen in four. Both hypercapnia and desaturation were seen in three patients in this group, while neither hypercapnia nor desaturation were seen in 15. These results did not reach the threshold of significance ($p = 0.27$).

Discussion

Surprisingly, HFNO did not significantly reduce the proportion of patients desaturating below a SpO_2 of 90% during EBUS at the expected degree of efficacy. While it is interesting that the primary outcome reached the threshold of statistical significance if analysed using a per-protocol approach, this result should be interpreted with caution as it was caused by the movement of a single patient between groups.

The significantly higher median nadir SpO_2 observed in the HFNO group suggests that, for patients with relatively normal airway and lung function HFNO produces superior oxygenation during conscious sedation. This was in contrast to previous findings, though the patients in this trial may have been less unwell than the patients in a previous trial of intensive care patients undergoing intubation [14].

While patients in each group experienced desaturation, only one of four desaturating patients in the HFNO group and two of 10 desaturating patients in the standard oxygenation group required the procedure be interrupted for specific airway management. This suggests that the desaturations were brief, and the treating anaesthetist felt that the patients remained safe during these episodes.

The results of the exploratory analysis may provide insight into the cause of the desaturation seen in the primary outcome. There are five main causes of desaturation; hypoventilation, shunt, V/Q mismatch, hypoxic mixture and diffusion impairment. Of these causes, increasing FiO_2 tends to improve V/Q mismatch, hypoxic mixture and diffusion impairment, and HFNO is likely to improve FiO_2. Increasing FiO_2 tends not to significantly improve hypoventilation or shunt. Hypoventilation tends to cause an increase in $EtCO_2$, while other causes of desaturation tend to not cause this increase. Hypoventilation in the studied group is most likely due to central ventilation depression caused by the anaesthetic agents. Moreover, some patients (such as CO_2 retainers) are prone to hypoventilation, leading to increased $ETCO_2$ when given supplemental oxygen, especially high flow 100% oxygen. We have previously demonstrated elevation of $PaCO_2$ to be a common event in bronchoscopy [15]. Procedure time is highly variable [15] depending on the techniques utilised [16], and is generally longer in EBUS than for standard bronchoscopy.

The results observed in the standard oxygenation group show that both hypercapnic and non-hypercapnic desaturation occurred, suggesting that both

hypoventilation and other causes of desaturation were present and not fully treated by the administered oxygen.

In the HFNO group, desaturation was only observed in conjunction with hypercapnia, suggesting that desaturation was driven by hypoventilation. This may be because by increasing the FiO_2 (and therefore P_AO_2), HFNO overcame other causes of desaturation.

Of interest, ten of the 23 patients analysed in the HFNO group were hypercapnic. Other studies have reported effective CO_2 clearance by HFNO, but this data suggests it is not completely effective at maintaining normal $EtCO_2$. It is possible that anaesthetists were reassured by the SpO_2 values, and did not intervene when patients hypoventilated, leading to the observed outcomes.

The data reinforces the point that HFNO does not provide total insurance against the development of hypoxaemia (particularly when driven by hypoventilation), and that some patients may be better managed by endotracheal intubation and ventilation for EBUS to prevent desaturation.

Although participants were not explicitly informed of their group allocation, it was not possible to remain blinded after the device was applied. Most of the outcomes were objective and well-defined, but there might be bias in subjective outcomes such as satisfaction scores.

The small size of the trial is also a limitation. The incidence of desaturation observed in the HFNO group was consistent with previous publications, at around 15%. However, the incidence of desaturation was lower than expected in the standard therapy group (33% rather than the expected 48%). A revised power calculation using the observed desaturation rate in both groups indicated that the trial had a power of only 46% for the given parameters, and that to achieve 80% power, 78 patients would have needed to be recruited in each arm. It is therefore likely that the trial was underpowered to detect a real, but smaller than anticipated difference between the techniques of oxygen administration. The patients enrolled in this trial may have been less vulnerable to hypoxaemia than those enrolled in previous trials. Future trials should re-calibrate the expected difference when calculating the sample size.

The trial did not explore other markers of ventilation adequacy such as partial pressure of arterial carbon dioxide, tidal volumes or minute ventilation, so the accuracy of hypercapnia as a marker of hypoventilation is unproven. Moreover, the

recorded value of the end-procedure $ETCO_2$, taken via a sampling line from the distal trachea, could have been affected by the method of oxygenation and gas flow used. This could also be a potential confounding factor.

The trial was a pragmatic, real-world exploration of the role of HFNO during EBUS. The results should be widely applicable to adults undergoing this procedure using conscious sedation. The trial did not enrol children or pregnant women, and is unable to guide practice in these patients, though these patients very rarely present for EBUS.

HFNO did not result in a significantly lower proportion of patients experiencing desaturation during EBUS compared to standard oxygen therapy. HFNO may not protect patients against hypoventilation-induced hypoxaemia nor hypercapnia. Further research is required to determine if the degree of benefit is smaller than expected in this trial.

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Table 1 Baseline characteristics and procedure data of 60 patients having high flow humidified nasal oxygenation (HFHNO) or standard oxygenation under sedation for endobronchial ultrasound (EBUS) procedure. Values are number (proportion), mean (SD) or median (IQR [range]).

	HFHNO n=30	Standard oxygenation n=30
Age; y	62.8 (14.1)	63.4 (14.3)
Sex; male	19 (63%)	19 (63%)
BMI; $kg.m^{-2}$	26.9 (5.8)	27.4 (6.4)
ASA physical status		
1	3 (10%)	2 (7%)
2	11 (37%)	8 (27%)
3	16 (53%)	19 (63%)
4	0 (0%)	1 (3%)
Co-morbidities		
Asthma	2 (7%)	3 (10%)
Chronic obstructive pulmonary disease	7 (23%)	8 (27%)
Bronchiectasis	0 (0%)	0 (0%)
Pulmonary fibrosis	1 (3%)	1 (3%)
Pulmonary carcinoma	2 (7%)	7 (23%)
Mesothelioma	0 (0%)	0 (0%)
Obstructive sleep apnoea	3 (10%)	2 (7%)
Obesity hypoventilation syndrome	0 (0%)	0 (0%)
Requiring CPAP at night	1 (3%)	1 (3%)
Requiring CPAP during day	0 (0%)	0 (0%)
Baseline SpO_2; %	96 (95-99)	96 (94-98)
Procedural data		
Procedural type		
Linear EBUS	25 (84%)	16 (53%)
Radial EBUS	4 (13%)	8 (27%)
Both	1 (3%)	6 (20%)
Total procedural time; min	24 (16-28 [11-41])	21 (17-32 [11-46])
Sedation agents used		
Propofol	18 (60%)	22 (73%)
Midazolam	11 (37%)	8 (27%)
Alfentanil	14 (47%)	18 (60%)
Fentanyl	0 (0%)	1 (3%)
Remifentanil	12 (40%)	8 (27%)
Minimum oxygen rate; $l.min^{-1}$	50 (50-50 [30-50])	10 (10-10 [10-40])
Maximum oxygen rate; $l.min^{-1}$	50 (50-50 [30-70])	10 (10-10 [10-50])

Table 2 Comparison of secondary outcomes between the high flow humidified nasal oxygenation (HFHNO) or standard oxygenation under sedation for endobronchial ultrasound (EBUS) procedure. Values are number (proportion) or median (IQR [range]).

	HFHNO n=30	**Standard oxygenation n=30**	**p-value**
SpO_2 after pre-oxygenation; %	100 (99-100 [93-100])	98 (97-99 [94-100])	0.0001
Lowest SpO_2 during procedure; %	97.5 (94-99 [77-100])	92 (88-95 [79-98])	0.0000
Number of hypoxic (SpO_2 < 90%) episodes			
0	26 (87%)	20 (67%)	
1	2 (7%)	7 (23%)	
2	0 (0%)	1 (3%)	0.33
4	1 (3%)	1 (3%)	
6	1 (3%)	1 (3%)	
Duration of desaturation (SpO_2 < 90%); s	129 (63-181 [1-228])	40 (18-91 [2-295])	0.48
End-procedure $ETCO_2$; mmHg	40 (34-56 [19-77])	37 (33-46 [20-53])	0.15
Patient satisfaction; (1=very satisfied to 5=very dissatisfied)	1 (1-2 [1-2])	1 (1-2 [1-2])	0.40
Proceduralist satisfaction; (1=very satisfied to 5=very dissatisfied)	1 (1-2 [1-5])	1 (1-2 [1-4])	0.19
Anaesthetist satisfaction; (1=very satisfied to 5=very dissatisfied)	1 (1-2 [1-4])	1.5 (1-2 [1-5])	0.28

TED Study CONSORT Diagram