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Automatic versus manual oxygen titration using a novel nasal high-flow device in medical inpatients with an acute illness: a randomised controlled trial

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ABSTRACT

Background Guideline recommendations state oxygen should be administered to acutely unwell patients to achieve a target oxygen saturation (SpO_2) range. The current practice of manual oxygen titration frequently results in SpO_2 outside of a prescribed range. The aim of this study was to assess the efficacy of automatic oxygen titration using a closed-loop feedback system to achieve SpO_2 within a prescribed target range

Methods An open-label randomised parallel group trial was undertaken comparing automatic oxygen titration using a novel nasal high-flow device to manual oxygen titration using nasal high flow. Medical inpatients requiring oxygen therapy in Wellington Regional Hospital, New Zealand with a prescribed target SpO_2 range of 88%–92% or 92%–96% were recruited and randomised equally between the interventions for a period of 24 hours. The primary outcome was the proportion of time spent with SpO_2 within the prescribed range.

Results 20 patients were included in the analysis. Automatic oxygen titration resulted in a median (IQR) 96.2% (95.2–97.8) of time within the target range compared with 71% (59.4–88.3) with manual titration; difference (95% CI) 24.2% (7.9% to 35%), p<0.001. There was a reduction in the time spent with SpO_2 ≥2% above and ≥2% below range in the automatic titration group, although the point estimate for the differences were small; −1% (−8.2% to −0.04%), p=0.017 and −2.4% (−11.5% to 0.3%), p=0.05 respectively.

Conclusions Nasal high-flow with automatic oxygen titration resulted in a greater proportion of time spent with SpO_2 in target range compared with manual titration.

Trial registration The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000901101).

Key messages

- Does nasal high-flow with automatic oxygen titration result in a greater proportion of time spent with oxygen saturation (SpO_2) within a prescribed target range compared to nasal high-flow with the standard practice of manual oxygen titration in medical inpatients?
- In this randomised controlled trial, automatic oxygen titration resulted in a significantly greater proportion of time spent with SpO_2 within target range.
- This is the first study to demonstrate that automatic oxygen titration using nasal high flow is superior to the current practice of manual oxygen titration based upon intermittent SpO_2 measurements in medical inpatients with an acute illness, reducing the potential risk of over and under oxygenation.

INTRODUCTION

Oxygen is commonly administered in hospital with the aim of treating hypoxaemia.[1] International guidelines recommend titration of oxygen in order to achieve a target peripheral oxygen saturation (SpO_2) range in acutely unwell patients.[2 3] Deviation from this target SpO_2 range results in progressive risk of harm[4]; an SpO_2 below 90% in a hospital ward setting is associated with a 2.4-fold increase in risk of in-hospital mortality[5] and the liberal administration of oxygen is associated with a 1% increase in risk of mortality per 1% increase in SpO_2 above 96%,[6 7] although recent studies have suggested equipoise.[8 9] A target SpO_2 range of 92%–96% is recommended by the Thoracic Society of Australia and New Zealand (TSANZ)[3] and a range of 94%–98% by the British Thoracic Society.[2] Both guidelines recommend a lower target range of 88%–92% in patients who are at risk of hypercapnic respiratory failure.[2 3]

In current clinical practice, manual oxygen titration based on intermittent SpO_2 measurement is used in order to achieve a prescribed target SpO_2 range. This process has remained unchanged for several decades, despite evidence that patients receiving oxygen

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frequently have an SpO_2 outside this range.[10] Recently, oxygen delivery systems using a closed-loop feedback system have been developed which enable continuous automated adjustment of a delivered oxygen concentration.[11–15] Studies of these devices have demonstrated patients spend a greater proportion of time with SpO_2 within target range compared with the standard practice of manual oxygen titration both in the emergency department (ED),[12] ward setting[13] and following abdominal and thoracic surgery.[11]

To date, studies of automated oxygen titration in adults have involved conventional low-flow oxygen. Nasal high flow (NHF) involves the delivery of heated, humidified gas at high flow via a wide bore nasal cannula. This method of oxygen delivery has a number of beneficial physiological effects[16–20] and is associated with a reduced risk of endotracheal intubation when compared with conventional oxygen therapy in patients with acute hypoxaemic respiratory failure.[21 22] As a result, NHF has become an established therapy for selected patients with hypoxaemia in the acute care setting.[23]

The Airvo 3™ device (Fisher and Paykel Healthcare, Auckland, New Zealand) is a novel NHF system which is able to automatically titrate the delivered oxygen concentration in order to achieve a user set target SpO_2 using a closed-loop feedback mechanism. This is achieved by automatic adjustment of the oxygen concentration using an intelligent algorithm that adapts output based on SpO_2 responsiveness. A prototype version of this device has demonstrated responsiveness to changes in SpO_2 outside a target range in a laboratory-based exercise test.[24] This is the first study to investigate the use of NHF with automatic oxygen titration in adults with an acute illness. This aim of this study was to compare NHF with automatic oxygen titration to NHF with manual oxygen titration in patients who had been admitted to hospital with an acute medical illness. Our hypothesis was that NHF with automatic oxygen titration would result in a greater proportion of time spent with SpO_2 within target range.

METHODS

Study design

This was an open-label randomised parallel group trial. The trial was run in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Patients. Members of the public were not involved with the design or conduct of this study.

Participants

Patients under the care of a medical team were eligible for inclusion if they had a clinician prescribed SpO_2 target range of 88%–92% or 92%–96%, as per TSANZ guidelines.[3]

Inclusion criteria: target SpO_2 92%–96%

- Current inpatient under the care of a medical or surgical team.
- Expected duration of admission >24 hours from enrolment.
- NHF therapy already commenced or treating physician decision to start NHF or requirement for ≥2 L/min low-flow oxygen.

Inclusion criteria: target SpO_2 88%–92%

- Current inpatient under the care of a medical or surgical team.
- Expected duration of admission >24 hours from enrolment.
- NHF therapy already commenced or treating physician decision to start NHF or requirement for ≥1 L/min low-flow oxygen.

Common exclusion criteria

- Age <18.
- Unable to tolerate a brief interruption in oxygen or high-flow therapy.
- Domiciliary use of CPAP or NIV.
- Diagnosis of obstructive sleep apnoea.
- Evidence of respiratory infection or colonisation with multidrug resistant bacteria, *Pseudomonas* species, *Burkholderia Cepacia* or mycobacteria.
- Suspected or proven infection with SARS-CoV-2 (COVID-19).
- Haemodynamic instability (systolic blood pressure <90 mm Hg or requirement for vasopressor or inotropic support).
- Patient receiving end of life care.
- Risk of barotrauma, as assessed by the investigator.
- Nasal or facial conditions precluding use of NHF.
- Intracranial trauma or trans-nasal neurosurgery (within 6 weeks).
- Any condition which limits the feasibility of continuous SpO_2 monitoring using a finger probe such as anatomical deformity or vascular compromise.
- Pregnancy or breast feeding.
- Cognitive impairment or impaired consciousness precluding informed consent.
- Implanted electronic medical device (including insulin pump, pacemaker, neurostimulator and implantable cardioverter-defibrilator).
- Any other condition which, at the investigator's discretion, is believed may present a safety risk or impact the feasibility of the study or the study results.

Exclusion criteria: target SpO_2 92%–96%

- Requirement for >40% oxygen at time of enrolment (equivalent to 5 L/min low-flow oxygen).
- Hypercapnia (PCO_2 >45 mm Hg) with or without acidosis.
- Presence of any risk factor for hypercapnic respiratory failure including: chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, chest wall deformity or neuromuscular disease and

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investigator considers 92%–96% to be an inappropriate SpO_2 target.

Exclusion criteria: target SpO_2 88%–92%

- Requirement for >35% oxygen at time of enrolment (equivalent to 4 L/min low-flow oxygen)
- Respiratory acidosis (pH <7.35 and PCO_2 >45 mm Hg).

Patients with compensated hypercapnia and a target SpO_2 range of 88%–92% could be included, however, those with an associated respiratory acidosis were excluded. The study protocol was amended to facilitate the inclusion of surgical patients due to difficulty with recruitment during the COVID-19 pandemic, however, this was ultimately not required and only medical patients were recruited. As the first study of NHF with automatic oxygen titration in the acute setting, eligibility criteria were designed to provide a study population representative of those who may receive NHF in clinical practice, while excluding those at greatest risk and those who require close monitoring in an intensive care setting.

Procedures

Patients under the care of a medical team who were receiving oxygen were identified by a study investigator and potentially suitable patients were provided with an information sheet and written informed consent was obtained. Baseline physical observations were recorded and a capillary blood gas was taken from the earlobe. Eligible participants were randomised 1:1 to NHF with automatic oxygen titration using the Airvo 3 device or NHF with manual oxygen titration using the Airvo 2 device (Fisher and Paykel Healthcare, Auckland, New Zealand) for a period of 24 hours. The Airvo 2 device is an established NHF device and is used as part of routine practice in Wellington Hospital.

The randomisation schedule was computer generated by the study statistician and incorporated into the Research Electronic Data Capture (REDCap)[25 26] study electronic database. The randomisation schedule was concealed from study investigators within the REDCap database. The treatment to which each participant was randomised was automatically displayed for each recruited participant at the point of randomisation. This was an open-label study in which both participants and investigators were aware of the treatment, blinding to treatment allocation was not possible due to the nature of the intervention.

An AirSpiral heated breathing tube (Fisher & Paykel Healthcare, Auckland, New Zealand) and Optiflow+ nasal cannula (Fisher & Paykel Healthcare, Auckland, New Zealand) was used in both groups. A laminated guide was attached to the NHF device in both groups specifying the prescribed target SpO_2 range and prompting intervention if SpO_2 was above or below range.

For both groups, at the start of the intervention period, a study investigator titrated the delivered oxygen concentration to achieve SpO_2 as close to the mid-point of the target range as possible. The initial flow was set to 35 L/min, or the same flow as used prior to randomisation if the participant was already receiving NHF. All other clinical care continued as usual and investigators had no input into patient management during the intervention period.

Automatic titration

In the automatic titration group, an adhesive finger sensor provided feedback to the NHF device and an additional sensor was placed on the contralateral hand which was connected to an independent pulse oximeter (sat 801+ Bitmos Düsseldorf, Germany). The Airvo 3 device screen displayed SpO_2, flow, temperature, FiO_2 and FiO_2 upper and lower limits. A logging box was connected to the Airvo 3 device which recorded data. The independent pulse oximeter was used as a safety measure. The device was able to automatically titrate the delivered oxygen concentration within a range of 10%, for example, between 25% and 35%. An alarm sounded on the device if the SpO_2 was below range while FiO_2 was at the upper limit, or if SpO_2 was above range at the lower FiO_2 limit, at which point nursing staff were able to increase the upper limit by 5% or reduce the lower limit by 5% as needed. High and low SpO_2 alarms (98% and 90%, respectively, with target range 92%–96% and 94% and 86%, respectively, with target range 88%–92%) were also set on the NHF device and independent pulse oximeter.

Manual titration

In the manual titration group, an adhesive finger sensor was connected to a data logging box which did not display SpO_2 or any other metrics. The Airvo 2 device screen displayed flow, FiO_2 and temperature. Nursing staff were instructed to measure SpO_2 according to usual practice; continuous oximetry was used at the discretion of the medical and nursing teams.

In both groups heart rate, SpO_2, FiO_2 and flow data were recorded by the data logging boxes every second, resulting in approximately 86 400 measurements per participant. At the end of the 24-hour study period, a second capillary blood gas was taken from the earlobe, the investigational NHF device was removed and data was downloaded and processed. In the manual titration group FiO_2 data analysis was assisted by visual inspection of the FiO_2-time plots due to noise in the Airvo 2 FiO_2 data. Participants were withdrawn from the study in event of a sustained requirement for >50% oxygen (92%–96% group), >40% oxygen (88%–92% group) or an increase of more than 10% from the FiO_2 at the start of the intervention period. Further withdrawal criteria are shown in the supplementary material.

An independent data safety monitoring committee (DSMC) reviewed the safety of the study after the first, second and third enrolled participants and every 10 participants thereafter. All adverse events were also

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reviewed by the DSMC. The study funder had no involvement with the DSMC.

Outcomes

The primary outcome was the proportion of time spent with SpO_2 within the prescribed target range. Data with adequate signal quality (defined as >0.5 on a scale from zero to one) were used for the primary outcome in order to reduce the likelihood of including spurious SpO_2 values resulting from motion artefact. Secondary outcomes included the proportion of time spent with SpO_2 within range irrespective of signal quality and the proportion of time spent ≥2%, ≥4% and ≥8% below range, as well as ≥2% and ≥4% above range. Additional secondary outcomes included heart rate, number of FiO_2 (manual titration) or FiO_2 range (automatic titration) adjustments, FiO_2 and capillary blood gas measures. Tertiary outcomes included the proportion of time spent with SpO_2 above range when the FiO_2 was at the lower limit and time spent with SpO_2 below range when the FiO_2 was at the upper limit (automatic titration group only), duration of hospital admission, number of medical emergency team (MET) calls and requirement for non-invasive ventilation or intensive care unit (ICU) admission.

Sample size

Based on two previous studies investigating a closed-loop control oxygen delivery system,[12 13] a total sample size of 46 participants was estimated to provide 90% power to detect a 30% difference in time spent in target range between intervention and control based on an SD of 30. The sample size calculations were based on using an unpaired t-test to compare groups, equal size numbers in intervention and control groups, and a two-sided type I error rate (alpha) of 5%. Due to uncertainty whether this sample size calculation was applicable to the performance of the NHF device, a prespecified sample size re-estimation was performed after 10 participants which indicated a revised total of 20 participants was required to provide at least 90% power to detect a 30% difference in time spent within target SpO_2 range. A minimum of 6 hours data was required for the participant to be included in the analysis. Additional participants were recruited to meet the sample size if less than 6 hours of data was collected. As a result, a per protocol analysis was undertaken in those participants in whom at least 6 hours of data was available.

Statistical analysis

The primary analysis was pre-specified as a general linear model (analysis of covariance, ANCOVA), however, due to a skewed data distribution, a Wilcoxon rank-based method with the Hodges-Lehmann estimator for location difference and appropriate confidence intervals was used for all outcomes relating to SpO_2. Other outcomes were analysed using ANCOVA with adjustment for baseline or by t-test where no baseline was appropriate. Mean (SD) values are presented for normally distributed variables and median (IQR) for other variables. SAS V.9.4 (SAS Institute) was used.

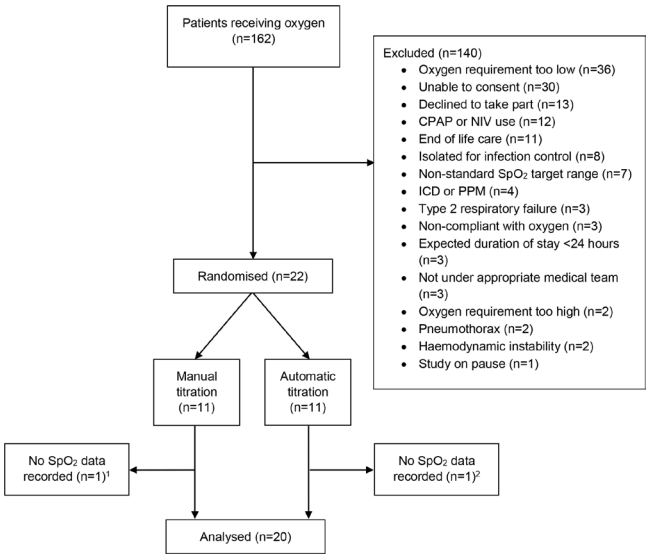

Figure 1 Consort flow diagram. [1]A technical fault caused no SpO_2 data to be recorded. [2]SpO_2 was found to be within range while breathing room air and the participant was withdrawn prior to starting the randomised treatment, as a result, no SpO_2 data were recorded. CPAP, continuous positive airway pressure; ICD, implanted cardioverter defibrillator; NIV, non-invasive ventilation; PPM, permanent pacemaker; SpO_2, oxygen saturation.

RESULTS

Participants were recruited to the trial between 9 January 2020 and 2 October 2020.[24] A total of 162 patients receiving oxygen were screened and 22 were randomised. Twenty participants with greater than 6 hours of recorded data were included in the per-protocol analysis. The overall mean (SD) duration of intervention for participants included in the analysis was 23.2 (2.1) hours and 22.4 (3.8) hours in the manual and automatic titration groups, respectively. One participant in the automatic titration group was withdrawn from the study after 12.3 hours due to an increase in oxygen requirement in excess of the protocol defined limit. There was a device fault for a different participant in the automatic titration group which resulted in an unexpected shut down of closed-loop control after 19.7 hours. Two participants in the manual titration group finished the intervention period after 17.5 hours and 22.5 hours, respectively, as the treating clinical team wished to stop oxygen therapy. The trial profile is shown in figure 1. Baseline participant characteristics are shown in table 1. Baseline and postintervention capillary blood gas values according to prescribed target range are shown in table 2. Participant characteristics and blood gas values were similar between treatment groups. The mean (SD) percentage of time

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Table 1 Baseline participant characteristics

Characteristic	NHF manual N=10	NHF automatic N=10
Sex		
Female	4	4
Ethnicity		
European	9	10
Pacific peoples	1	0
Reason for oxygen		
Exacerbation of asthma	2	1
Exacerbation of COPD	3	3
Heart failure	1	1
Interstitial lung disease	1	1
Pulmonary embolism	1	0
Pneumonia	2	4
Target SpO_2 range		
88%–92%	5	6
92%–96%	5	4
High-dependency area		
Yes	5	4
	Mean (SD)	
Age (years)	69.2 (19)	68.7 (17)
Heart rate (beats/min)	80.2 (17.2)	89.9 (15.1)
Respiratory rate	21.7 (3.3)	23.4 (5.9)
Systolic blood pressure	130 (20)	118.1 (16.1)
Diastolic blood pressure	70.4 (9)	72.3 (10.7)
Baseline FiO_2 (%)	30.6 (3.5)	28.3 (2)

COPD, chronic obstructive pulmonary disease; FiO_2, fractional inspired oxygen; SpO_2, oxygen saturation.

with adequate signal quality was high and similar between the two interventions; 96.1 (2.9)% and 91.3 (5.8)% in the automatic and manual titration groups, respectively.

For the primary outcome, the automatic titration group spent a median (IQR) of 96.2% (95.2–97.8) of the intervention period with SpO_2 within target range, compared with 71% (59.4–88.3) in the manual titration group. The difference (95% CI) between the groups was 24.2% (7.9% to 35%), p<0.001; table 3 and figure 2. This difference was 24.3% (11.7 to 37.6), p<0.001 when all SpO_2 data, irrespective of signal quality was used for analysis.

For the secondary outcomes, there was a trend towards a reduction in time spent with SpO_2 ≥2% below range in the automatic titration group; difference −2.4% (−11.5 to 0.3), p=0.05 and a significant reduction in time spent with SpO_2 ≥2% above target range; difference −1% (−8.2 to −0.04), p=0.017. The maximum delivered oxygen concentration during the intervention period was significantly higher in the automatic titration group; mean difference adjusted for baseline (95% CI) 7.1% (4.6% to 9.7%), p<0.001. There was no difference in blood gas measurements or in the other secondary outcomes between interventions. Primary and secondary outcomes are summarised in table 3 and online supplemental table S1. Histogram density plots for individual participants according to randomised treatment and target SpO_2 range are shown in figures 3 and 4.

For the tertiary outcomes, the mean (SD) duration of hospital admission was 4.8 (2.6) days in the manual titration group and 8.1 (6) days in the automatic titration group. In the automatic titration group the median (IQR) percentage of time spent with SpO_2 below target range and FiO_2 at the upper limit was 1.1% (0.6–2.5) and with SpO_2 above range and FiO_2 at the lower limit was 0.2% (0–1.3).

Two post hoc analyses were performed. First, a subgroup analysis for the primary outcome according to target SpO_2 range demonstrated a greater proportion of time spent in target range for the automatic titration group in both the 88%–92% target range and the 92%–96% target range; difference 28.1% (6.9–45.4), p=0.018% and 23.3% (−10.3 to 5.2), p=0.028 respectively. Asymptotic assumptions were not met for the small samples hence confidence intervals do not correspond well to p values. Second, an analysis of proportion of time spent in target range during day and night (23:00–07:00 hour) demonstrated consistent performance of automatic titration with median (IQR) 96.6% (93.9–98.5) and 96.3% (93.6–98.1), respectively. In the manual titration group a higher proportion of time was spent in range during the day compared with overnight 77.5% (65.3–85.1) and 66.6% (46.4–85.4), respectively.

There was one MET call, one ICU admission and one death involving the same participant in the automatic titration group. This was considered to be a serious adverse event which was reviewed by the DSMC, and was determined to be unrelated to the study intervention. The device fault which occurred in a different participant in the automatic titration group, causing an unexpected shut down of closed-loop control, was also reviewed by the DSMC. This did not lead to any adverse effects for the participant and the fault was remedied by a software update prior to further participant recruitment.

DISCUSSION

This trial demonstrates medical inpatients with an acute illness spend 96% of time with SpO_2 within a prescribed target range while receiving oxygen delivered using NHF with automatic oxygen titration. This is significantly higher than the 71% of time spent within target range using NHF with manual oxygen titration, which is current standard practice. Over the 24-hour intervention period, this equates to approximately six additional hours spent with SpO_2 within target range, which may be of clinical importance.

The reduction in time spent with SpO_2 ≥2% above and below target range with automatic titration suggests that

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Table 2 Baseline and postintervention capillary blood gas results

	NHF manual			NHF automatic		
Target SpO_2 range	88%–92% N=5	92%–96% N=5	All N=10	88%–92% N=6	92%–96% N=4	All N=10
Baseline	**Mean (SD)**					
pH	7.44 (0.02)	7.47 (0.06)	7.5 (0)	7.46 (0.06)	7.47 (0.02)	7.5 (0)
PCO_2 (mm Hg)	35.9 (6.2)	30.5 (4.9)	33.2 (6)	40.0 (7.0)	32.6 (5.2)	37 (7.1)
PO_2 (mm Hg)	59.0 (4.7)	68.9 (9.3)	63.9 (8.7)	62.6 (12.9)	68.9 (6.9)	65.1 (10.9)
Target SpO_2 range	88%–92% N=5	92%–96% N=5	All N=10	88%–92% N=6	92%–96%* N=3	All* N=9
Postintervention	**Mean (SD)**					
pH	7.46 (0.02)	7.47 (0.05)	7.5 (0)	7.47 (0.04)	7.47 (0.02)	7.5 (0)
PCO_2 (mm Hg)	35.9 (6.1)	30.7 (6.2)	33.3 (6.4)	40.4 (6.5)	34.0 (4.7)	38.2 (6.5)
PO_2 (mm Hg)	56.6 (5.6)	73.4 (12.6)	65 (12.8)	56.1 (6.0)	74.2 (8.7)	62.1 (11.1)

*One participant in the automatic titration 92%–96% group was withdrawn and subsequently required mechanical ventilation, hence an end of intervention blood gas was not taken.
NHF, nasal high-flow; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen.

this novel device has the potential to reduce the risks associated with both hypoxaemia and hyperoxaemia. Although the point estimates for this difference were small, there was large variability in the manual titration group, illustrated by the wide IQR for these outcomes and correspondingly wide CIs for the difference. In comparison, there was a consistent reduction in time spent outside of range in the automatic titration group, well illustrated in the histogram density plots in figures 3 and 4 where a tall narrow distribution around the target range was observed for automatic titration and a more variable wider distribution for manual titration. The greater proportion of time spent with SpO_2 ≥2% above compared with below range in the manual titration group suggests that healthcare professionals aim for a margin of comfort with the delivery of oxygen therapy, even with a specified target SpO_2 range. The mean number of manual FiO_2 adjustments in the manual titration group was comparable to the number of FiO_2 range adjustments performed by nursing staff in the automatic titration group, suggesting that for a similar degree of nursing staff input, a significantly greater proportion of time with SpO_2 in target range can be achieved. Although not evaluated in this study, automatic oxygen titration may reduce the nursing

Table 3 Outcomes

	NHF manual N=10	NHF automatic N=10	Difference (95% CI)	
Outcome	Median (IQR)		Rank based	P value
Time in target SpO_2 range (%)	71 (59.4 to 88.3)	96.2 (95.2 to 97.8)	24.2 (7.9 to 35)	<0.001
Time in target SpO_2 range—all SQ (%)	69 (52 to 82.4)	93.3 (89.7 to 97.1)	24.3 (11.7 to 37.6)	<0.001
Time ≥2% above range (%)	5.6 (9)	0.8 (2.2)	−1 (−8.2 to −0.04)	0.017
Time ≥4% above range (%)	0 (0 to 0.4)	0 (0 to 0)	−0.01 (−0.25 to 0)	0.021
Time ≥2% below range (%)	1.5 (0.5 to 8.2)	0.1 (0 to 0.2)	−2.4 (−11.5 to 0.3)	0.05
Time ≥4% below range (%)	0 (0 to 0.3)	0 (0 to 0)	−0.25 (−4.8 to 0.4)	0.31
Time ≥8% below range (%)	0.1 (0 to 1.6)	0.1 (0 to 0.2)	−0.01 (−1.5 to 0.1)	0.54
	Mean (SD)		**Mean difference***	
Mean heart rate (beats/min)	78 (13.1)	87.9 (15.1)	0.5 (−8.2 to 9.1)	0.91
Mean FiO_2 (%)	29.4 (3.5)	29.1 (2)	1.5 (−0.5 to 3.4)	0.13
Minimum FiO_2 (%)	25.3 (4.2)	23.3 (2.6)	−0.5 (−3.5 to 2.6)	0.76
Maximum FiO_2 (%)	32 (4.3)	37.1 (2.7)	7.1 (4.6 to 9.7)	<0.001
No of manual FiO_2 changes†	4.8 (5.4)	4 (3.9)	−0.8 (−5.3 to 3.7)	0.35
No of automatic FiO_2 changes	N/A	72 103 (15118)	N/A	N/A

*Adjusted for baseline, other than number of manual FiO_2 changes.
†In the automatic group the number of manual FiO_2 changes refers to the number of times the FiO_2 limits were changed by nursing staff.
FiO_2, fractional inspired oxygen; NA, not available; NHF, nasal high-flow.

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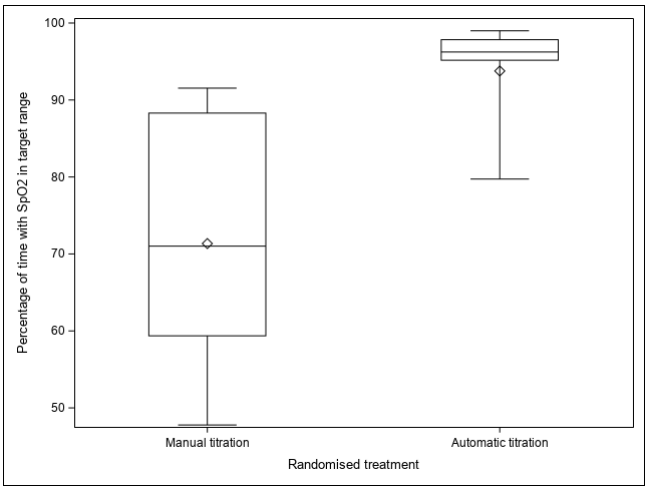

Figure 2 Box plot of proportion of time spent with SpO_2 in target range according to randomised treatment. On the box-plots the symbol is the mean, the horizontal lines are the 25th, 50th (median) and 75th percentiles, and the whiskers extend from the minimum to maximum values. SpO_2, oxygen saturation.

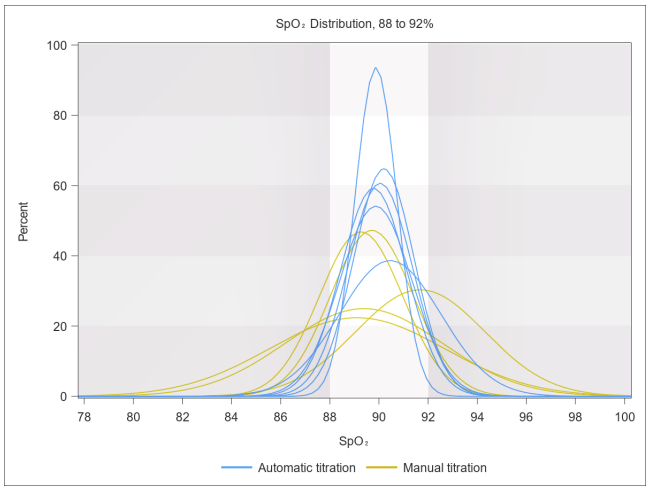

Figure 4 Histogram density plot of SpO_2 measurements during the intervention period for individual participants with a target range of 88%–92%. The lightly shaded area respresents the target range. SpO_2, oxygen saturation.

time spent at the bedside titrating oxygen, freeing nursing resources for other aspects of clinical care.

Compared with our results, previous studies of conventional oxygen therapy with automatic titration have demonstrated a lower mean 81.2% and 81.3% proportion of time spent with SpO_2 in target range in patients admitted to hospital with an acute exacerbation of COPD[13] and hypoxaemic patients in the ED,[12] respectively. The manual titration group of these studies also spent a lower proportion of time in range, 51.3 (19.7)%[13] and 51.8 (30)%[12] as compared with the manual titration group in this study. This may be due to the relatively high proportion of participants who were in a high-dependency area where continuous oximetry is typically used, differing participant characteristics or the presence of a bedside guide indicating target SpO_2 range and prompting intervention if SpO_2 was out of range in this study.

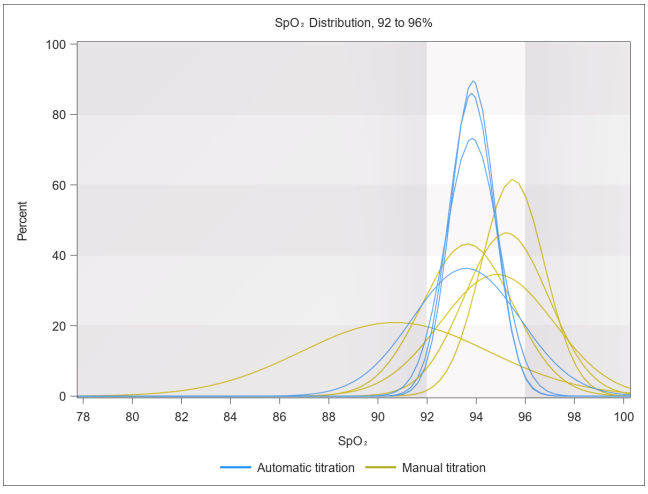

Figure 3 Histogram density plot of SpO_2 measurements during the intervention period for individual participants with a target range of 92%–96%. The lightly shaded area respresents the target range. SpO_2, oxygen saturation.

The strengths of this study include the use of NHF in both groups, ensuring any differences are due to the mechanism of oxygen titration. In addition, oxygen was titrated at the start of the intervention period to ensure all participants were within target range ensuring a fair starting point. However, there are a number of considerations when interpreting the results. First, while the study was adequately powered for the primary outcome variable, it was underpowered to detect a difference between interventions in terms of significant time exposure to marked over or under-oxygenation. The study was also not powered to detect differences in clinical outcomes. Second, the participants included had mild to moderate hypoxaemia and so are not generalisable to a population with greater oxygen requirements or who are more unstable. Patients requiring more than 40% oxygen were excluded from this study, a group likely to benefit from NHF therapy,[22] however, this exclusion criterion was used to enhance safety as this study was the first time this novel method of oxygen delivery had been used in an inpatient setting. Lastly, the continuous display of SpO_2 and use of alarms in the automatic titration group may have alerted nursing staff to deviation from the target range more rapidly than in the manual titration group, where continuous oximetry was used at the discretion of the nursing and medical team. These factors are, however, an intrinsic part of the automatic titration system and can be viewed as an advantage over standard care. The potential issue of 'alarm fatigue' will need to be addressed in future studies over a longer duration of intervention.

In conclusion, this study provides evidence that NHF with automatic oxygen titration using the Airvo 3 device results in a greater proportion of time spent with SpO_2 within target range compared with NHF with manual

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oxygen titration in medical patients with hypoxaemia. These results need confirmation in larger studies and in different patient populations and clinical settings. Further investigation as to whether the use of nasal high flow with automatic oxygen titration influences clinical outcomes such as escalation of care and hospital length of stay is also warranted.

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Contributors JH, RB and IB designed the study. JH was principal investigator and NK and GB were investigators. NS designed and maintained the electronic study database. AE and MW performed the data processing and statistical analysis. JH wrote the first draft of the manuscript and all authors contributed to the final version.

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Competing interests JH reports personal fees from Fisher and Paykel Healthcare, outside the submitted work. RB reports a grant from Fisher and Paykel Healthcare to undertake this study.

Patient consent for publication Not required.

Ethics approval The trial was approved by the Northern A Health and Disability Ethics Committee.

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Data availability statement Data are available on reasonable request. Individual participant data that underlie the results reported in this article, after deidentification(text, tables, figures and appendices) will be avaliable one year after publication until a minimum of 5 years after publication to researchers who provide a methodologically sound proposal that has been approved by the study steering committee and sponsor to achieve the aims outlined in the approved proposal. This is possible through a signed data access agreement and subject to approval by the principal investigator (james.harper@mrinz.ac.nz) and the study sponsor (james.revie@fphcare.co.nz). No other documents will be available.

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