Randomised cross-over study of automated oxygen control for preterm infants receiving nasal high flow

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ABSTRACT

Objective To evaluate a prototype automated controller (IntellO$_2$) of the inspired fraction of oxygen (FiO$_2$) in maintaining a target range of oxygen saturation (SpO$_2$) in preterm babies receiving nasal high flow (HF) via the Vapotherm Precision Flow.

Design Prospective two-centre order-randomised cross-over study.

Setting Neonatal intensive care units.

Patients Preterm infants receiving HF with FiO$_2$ ≥25%.

Intervention Automated versus manual control of FiO$_2$ to maintain a target SpO$_2$ range of 90%–95% (or 90%–100% if FiO$_2$=21%).

Main outcome measures The primary outcome measure was per cent of time spent within target SpO$_2$ range. Secondary outcomes included the overall proportion and durations of SpO$_2$ within specified hyperoxic and hypoxic ranges and the number of in-range episodes per hour.

Results Data were analysed from 30 preterm infants with median (IQR) gestation at birth of 26 (24–27) weeks, study age of 29 (18–53) days and study weight 1080 (959–1443) g. The target SpO$_2$ range was achieved 80% of the time on automated (IntellO$_2$) control (IQR 70%–87%) compared with 49% under manual control (IQR 40%–57%; p<0.0001). There were fewer episodes of SpO$_2$ below 80% lasting at least 60 s under automated control (0 (IQR 0–1.25)) compared with manual control (5 (IQR 2.75–14)). There were no differences in the number of episodes per hour of SpO$_2$ above 98% (4.5 (IQR 1.8–8.5) vs 5.5 (IQR 1.9–14); p=0.572) between the study arms.

Conclusions The IntellO$_2$ automated oxygen controller maintained patients in the target SpO$_2$ range significantly better than manual adjustments in preterm babies receiving HF.

Trial registration number NCT02074774.

What is already known on this topic?

- Many neonatal units target higher SpO$_2$ ranges (eg, 90%–95%) for preterm babies.
- Automated control devices have been shown to improve SpO$_2$ targeting.
- Hypoxic episodes with SpO$_2$ <80% for ≥60 s are associated with poorer outcomes in preterm infants.

What this study adds?

- The IntellO$_2$ device significantly improved the time spent in SpO$_2$ target range from 49% under manual control to 80% under automated control.
- Under automated control there were fewer and shorter episodes of SpO$_2$ <80% for ≥60 s.
- There were overall reductions in the proportion of time in hypoxic and hyperoxic SpO$_2$ under automated control, with more time spent in air.

INTRODUCTION

A recent meta-analysis from the NeoProm Collaboration confirmed that a lower SpO$_2$ range was associated with a higher risk of death and necrotising enterocolitis.[1] As a result, many neonatal units, including our own, target a higher range of SpO$_2$, for example, 90%–95%. For staff, maintaining SpO$_2$ targets presents a compliance challenge.[2] Avoiding both hypoxia and hyperoxia is an important goal.[3] While additional training improves compliance,[4] manual maintenance of the target range 90%–95% may only be achieved less than 50% of the time.[5]

A meta-analysis concluded that improved targeted SpO$_2$ with reduced hypoxia and hyperoxia can be achieved using automated control of inspired oxygen concentration (FiO$_2$) in babies requiring both invasive and non-invasive ventilation (NIV).[6]

This study evaluates a new device (IntellO$_2$, Vapotherm, USA) which controls the Precision Flow (Vapotherm, USA) delivering nasal high flow (HF). We hypothesised that, for preterm babies on HF, the IntellO$_2$ would maintain an SpO$_2$ target range of 90%–95% for a greater percentage of time compared with standard (manual) practice.

METHODS

Study design and setting

Our study was a prospective, two-centre, order-randomised, cross-over trial of HF employing automated versus manual oxygen titration, conducted in the neonatal intensive care units (NICU) at St Peter's Hospital, Surrey, UK, and Oxford University Hospitals NHS Foundation Trust, Oxford, UK. Both units predominantly use HF in preference to nasal continuous positive airway pressure (CPAP) for NIV according to published guidelines.[7–9] Staff received device and study protocol training, including a reminder of the importance of maintaining SpO$_2$ targets. Written parental consent was obtained for all patients.

Study patients

Patients were eligible to participate if they were preterm and receiving HF at FiO_2 ≥25%. An a priori inclusion criterion was that patients would require at least 12 adjustments of FiO_2 during the manual arm to ensure adequate algorithm testing.[10] This would only be apparent once the manual arm had been completed. Exclusion criteria were: (A) presence of major congenital abnormalities; (B) haemodynamic instability; (C) seizures; (D) ongoing sepsis; (E) meningitis; or (F) clinician's concern regarding infant stability. By these criteria, we aimed to avoid studying babies whose clinical condition was either deteriorating or improving at a rate that would have impacted on the 48 hours' study window. Nursing staff were very experienced in the use of HF in the study population and manual adjustments would reflect their standard practice. In accordance with UK practice the ratio of nurse to patient was 1:2 or 1:3.

IntellO$_2$ device

The IntellO$_2$ works with the Precision Flow, using a modified closed-loop control algorithm,[11] employing pulse oximetry as the primary input signal with signal averaging set at 8 s (Masimo, Irvine, USA) to target a user-set SpO_2 value. Further details are provided in online supplementary appendix 1.

Study protocols

Babies were randomised to commence either on manual or automated mode. SpO_2 (alarm range 90%–95%) was continuously monitored on the NICU monitors as per normal standard of care[12]; a second pulse oximetry probe was placed initially on the right wrist for the IntellO$_2$ input. Staff were instructed to care for the baby normally in both study arms, including SpO_2 probe repositioning.

In manual mode, all FiO_2 adjustments were made by clinical staff as needed. In automated mode, FiO_2 was adjusted by the IntellO$_2$, set to maintain a single SpO_2 value of 93%. Staff could adjust all settings, including oxygen, in both modes, depending on clinical judgement.

In both arms, data for FiO_2, SpO_2, pulse rate, flow, mode and manual adjustments were logged by the IntellO$_2$. Staff recorded the time and reason for all manual oxygen adjustments, as well as any cares or procedures which could affect SpO_2. The study period in each arm was 24 hours' run consecutively.

The primary outcome was the time in target SpO_2 range 90%–95% (90%–100% if FiO_2=21%) by pulse oximetry. Secondary outcomes included the number of episodes of SpO_2 below 80% lasting at least 60 s, duration and frequency of episodes with SpO_2 above 95% or below 90%, frequency of FiO_2 adjustments, and overall mean FiO_2 and flow.

Statistical design and analysis

A sample requirement of 30 patients was determined based on a pilot study (Saslow JG; unpublished) to provide 90% power, and 0.05 significance (two sided) to show difference of 19% in time spent within target SpO_2 range. Each subject acted as their own control. The study was defined as intention to treat, thus manual adjustments in the automated arm would be included in that arm. Quantification of SpO_2 episodes above, in and below the target range was performed. Mean flow (L/min) and FiO_2 were calculated for each patient over the 24 hours' study period. The known limitations of the Precision Flow device, where displayed FiO_2 21%–23% delivers FiO_2=21%, and displayed FiO_2 98%–100% delivers FiO_2=100%, were accounted for in the analysis. Babies were not deemed to be 'out of range' if their SpO_2 was above 95% and their FiO_2 was 21%, in line with clinical practice.

Subjects were block randomised using statistical software, and assignments were maintained in consecutively numbered opaque envelopes until randomisation and assignment to treatment arm by the consenting researcher. Statistical analysis was performed using Wilcoxon signed-rank test, with findings reported as median values with IQRs (median (IQR)), unless otherwise annotated. Ranges are also reported for demographics. Categorical variables are presented as proportion of subjects in each category. Statistical significance was accepted where $p<0.05$. Analyses were performed using MedCalc (V.18, MedCalc Software, Brussels, Belgium) and Minitab (V.18.1, Minitab, PA, USA).

The study was registered at ClinicalTrials.gov NCT02074774. Independent Data Safety Monitoring Board (DSMB) review was undertaken at two points during the study.

Table 1 Patient demographics

Patient characteristics	Median (IQR)	Range
Gestation age at birth (weeks)	26 (24–27)	23–32
Birth weight (g)	793 (606–918)	378–2100
Age at time of study (days)	29 (18–53)	5–109
Weight at time of study (g)	1080 (959–1443)	576–2318
Males, n (%)	13 (43)	–

Data presented as median (IQR) and range (min-max), except for gender, for n=30.

RESULTS

Demographics

Data sets from 30 different patients with mean gestational age of 26.4 weeks were evaluated for the recruitment period of December 2016 to November 2017. Patient characteristics are presented in table 1.

Data analysis

Seven data sets were excluded from five subjects. Additionally six different patients had some issues during the study; these are described in more detail in online supplementary appendix 2. After discussion with the DSMB they were included in the analysis on an intention-to-treat basis.

Time in target SpO_2 range

Babies in the automated arm spent significantly more time in the target range versus the manual arm (automated 80% (70–87) vs manual 49% (40–57); $p<0.0001$). Figure 1 shows the pooled histogram for SpO_2, with 93% as the most common SpO_2 in both study arms. Figure 2 shows the histogram of FiO_2 values for all patients in both study arms. There was less variation for the SpO_2 values in the automated arm versus the manual (coefficient of variation, respectively, 0.03 (0.03–0.04) vs 0.06 (0.05–0.07); $p<0.00001$). The most common FiO_2 in automated mode was 21% (range 21–100) versus FiO_2 of 30% in manual mode (range 21–73). Babies had more episodes per hour within the target SpO_2 range in the automated arm (54 events/hour (39–62) vs 39 events/hour (34–48); $p=0.0002$) with similar episode durations between the arms (45 s (36–74) vs 43 s (26–56); $p=0.025$).

Improvement for time in target range

All babies showed improvements in time spent in the SpO_2 target range with mean improvement of 30% (range 10%–60%) (figure 3).

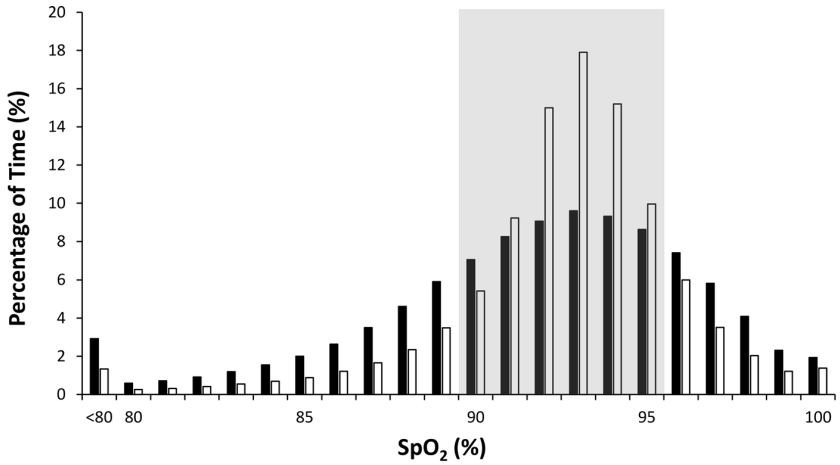

Figure 1 Composite SpO_2 histogram of all patient data (n=30) with paired bars as automated control (white) and manual control (black). The frequency of SpO_2 values denotes the proportion of total time (%) spent at each SpO_2, with aggregated SpO_2 values <80%. The target SpO_2 range for babies receiving oxygen (90%–95%) is illustrated by the shaded region.

Hypoxia and hyperoxia

The babies spent less time at any SpO_2 below the target range (12% vs 28%; p<0.0001) and specifically less time at SpO_2 <80% (0.5% vs 2.3%; p<0.0001) during automated control. There were no differences in the number of episodes below the target range, but they were of shorter duration in the automated arm as compared with the manual arm (17 vs 42 s; p<0.0001). There were fewer episodes of SpO_2 below 70% in the automated arm (0.21 vs 0.98 episodes/hour; p<0.001), of slightly shorter average duration (11 vs 14 s; p=0.0006). Likewise, babies spent a lower proportion of time with SpO_2 >95% in the automated versus manual arm (12% vs 23%; p<0.0001). There were more oversaturation episodes in the automated arm than the manual arm (37 vs 18 episodes/hour; p<0.0001) but the episodes were shorter in duration (12 vs 48 s; p<0.0001). At SpO_2 above 98% there were no differences in the episode frequency. These data are presented in table 2.

Occurrence of hypoxia within 60–180 s after a return to FiO_2=21% was higher in the automated arm compared with the manual arm (10 events/hour (5–18) vs 0 (0–0.1); p<0.001). Likewise following this event, hyperoxia within 60–180 s after a return to FiO_2=21% was also higher for the automated arm compared with the manual arm (8 events/hour (3–15) vs 0 (0–0.1); p<0.001). Overshoot, defined as hyperoxia lasting at least 5 s above SpO_2 range following hypoxia, was higher (as % of total study time) in the automated group (13% (6–18) vs 8% (3–19); p=0.021), but the episodes were shorter.

Flow and FiO_2

There was no difference in flow between automated and manual control (6.0 (5.0–6.6) L/min vs 5.8 (4.9–7.0) L/min; p=0.2790). The mean FiO_2 was greater in the automated arm than in the manual arm (34% (0.29–0.38) vs 29% (0.27–0.36); p<0.0001). The FiO_2 at the start of each patient study ranged from 25% to 53%.

Adjustments to FiO_2

The overall dynamics of adjustments to FiO_2 were different between automated and manual modes. There were more FiO_2 adjustments per hour during the automated versus manual mode (96 (93–101) adjustments/hour vs 1.6 (1.1–2.4) adjustments/

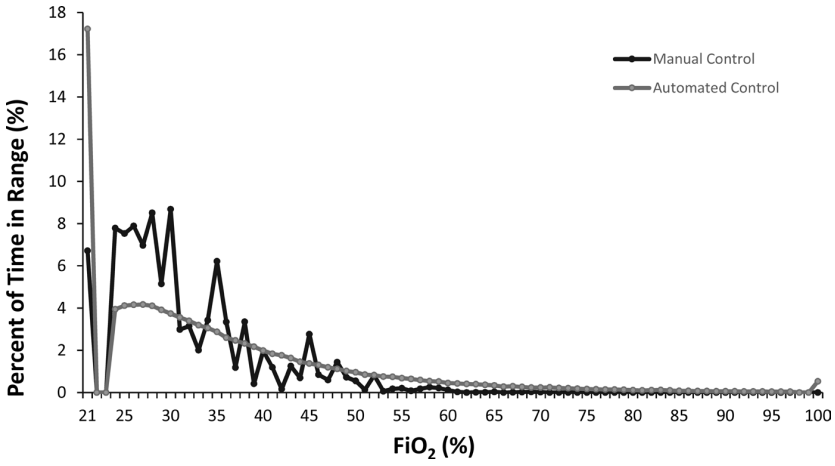

Figure 2 Proportion of all patient data (n=30) as a percentage of total study duration in each arm by FiO_2 (%). Values for automated control (grey) and manual control (black) are shown for each 1% FiO_2 interval.

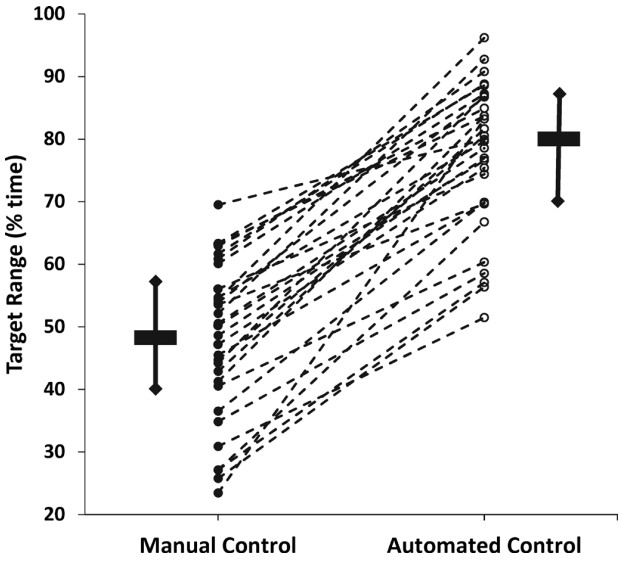

Figure 3 Comparison of percent time in target range of paired manual and automated control. Individual paired values (connected by line) denote the same patient. All completed patients shown (n=30). Horizontal bars denote the median of the associated control arm data. Vertical bars denote the IQR. Data represent the SpO_2 target range 90%–95% (or 90%–100% if FiO_2=21%).

hour; p<0.0001). Manual 'over-ride' adjustments of FiO_2 during automated mode occurred less than 0.001% of the time, and the median number of FiO_2 'over-ride' adjustments was 0 (0–1), with range 0–11. Three patients had one manual adjustment during automated mode. Three patients had two manual adjustments during automated mode. Fewer manual adjustments were made in automated versus manual mode (p<0.0001).

Table 2 Oxygen saturation range compliance

Category	Automated control	Manual control	P values*
Target SpO_2 range†			
Episodes/hour (counts)	41 (32–52)	38 (32–46)	0.0387
Average episode duration (s)	70 (49–99)	48 (31–61)	<0.0001
Per cent time in range (%)	80 (70–87)	49 (40–57)	<0.0001
SpO_2>95%‡			
Episodes/hour (counts)	37 (30–46)	18 (13–25)	<0.0001
Average episode duration (s)	12 (9.5–14)	48 (34–68)	<0.0001
Per cent time in range (%)	12 (8.9–16)	23 (15–41)	<0.0001
SpO_2>98%‡			
Episodes/hour (counts)	4.5 (1.8–8.5)	5.5 (1.9–14)	0.572 (NS)
Average episode duration (s)	6.4 (5.1–7.0)	24 (20–32)	<0.0001
Per cent time in range (%)	0.68 (0.29–1.4)	3.7 (1.2–9.9)	<0.0001
SpO_2<range			
Episodes/hour (counts)	27 (22–30)	24 (21–26)	0.082 (NS)
Average episode duration (s)	17 (15–21)	42 (29–50)	<0.0001
Per cent time in range (%)	12 (8.8–17)	28 (17–36)	<0.0001
SpO_2<80% for ≥60 s			
Total number of episodes§	0 (0–1.3)	5 (2.8–14)	<0.0001
Average episode duration (s)¶	0 (0–69)	119 (97–148)	<0.0001

Data presented as median (IQR) for n=30.
*Statistical analysis comprised Wilcoxon signed-rank test.
†Target range defined as SpO_2≥90% if FiO_2=21% or SpO_2 90%–95% if FiO_2>21%.
‡Data for above range categories reported for FiO_2>21%.
§The range (min-max) is (0–10) for automated and (1–38) for manual control.
¶The range (min-max) is (0–118) s for automated and (60–191.3) s for manual control.
NS, not significant.

Example of patient SpO_2 and FiO_2 traces

Figure 4 depicts examples of 24 hours' SpO_2 and FiO_2 traces (automated and manual modes) from two babies labelled A and B. Baby A was born at 26+6 weeks and recruited into the study on day 13 in an initial FiO_2=38% and flow of 6.0 L/min. Baby B was born at 23+3 weeks, with the study commenced on day 54, in FiO_2=34% on a flow of 6 L/min. The graphs demonstrate the variability in both SpO_2 and FiO_2 over the 24 hours' study periods, with greater variability in SpO_2 in manual mode and greater variability in FiO_2 in automated mode. Note the rising FiO_2 in baby B automatically applied to maintain a stable SpO_2 range. The baby was maintained on HF throughout and the following day completed the manual arm.

DISCUSSION

Under automated control by the IntellO_2 the babies in this study spent 31% more time in the target SpO_2 range (80% vs 49%), which was a significant improvement and supported the first part of the study hypothesis. Patients also spent less time in hypoxic or hyperoxic SpO_2 ranges under automated control. Every baby showed an improvement in their SpO_2 targeting although we did not identify why some showed greater improvements than others. In a recent systematic review, SpO_2 targeting compliance was also improved during automated control, both in infants being mechanically ventilated as well as NIV, with a total mean difference of 12.9% (range 6.5%–19.2%).[6]

Plottier *et al* studied 20 preterm babies on HF or CPAP and showed a 25% improvement in SpO_2 targeting compared with manual control, with reductions in hypoxia and hyperoxia.[13] In their study, the automatic arm was 4 hours' duration, with a researcher present throughout. In our study, the babies received normal nursing care and interventions with no additional staff present, with each arm running for 24 hours, including weekends. Like Plottier *et al*, our study was unblinded, and it is possible that our nursing staff controlled the SpO_2 range in the manual arm more diligently as they were aware that the values were being recorded, although this would be expected to have the effect of reducing the magnitude of any differences seen. Manual targeting of SpO_2 to a precise range is difficult, and a systematic review showed that while compliance was generally low (about 33%–54%)[2] it can be improved by improving the nurse to patient ratio.[14] In our study, 73% had a 1:2 care ratio and 17% a 1:3 care ratio (not recorded in 10%). The higher care ratios in the majority, and the high starting FiO_2 in many babies, give an indication that while they were sufficiently stable to be enrolled, many had considerable oxygen requirements and nursing workload. We reported flow as it is an important variable in babies receiving HF and is, along with FiO_2, a proxy for respiratory stability.

The IntellO_2 reduced the amount of time babies spent below the target range, especially at SpO_2 less than 80% mainly through reducing the duration of episodes rather than their frequency. Poets *et al* described the significantly increased risks of death or developmental delay in babies with hypoxia where the episodes lasted for 60 s or more.[15] Hypoxic episodes were generally short in both arms, but we specifically examined SpO_2 values below 80% lasting for a minute or more, and found a reduction during the automated arm. Hypoxia increases the risks of mortality and necrotising enterocolitis[1]; our study was not designed to detect these important but infrequent events.

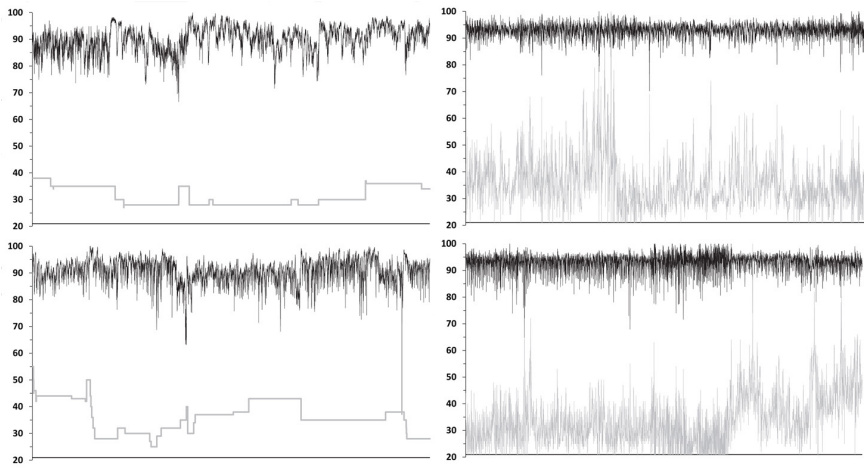

Figure 4 Top row Baby A. Bottom row Baby B. Complete 24 hours' recordings for each arm. Left manual control and right automated control recordings of SpO_2 (black line; y-axis is SpO_2) and FiO_2 (grey line, y-axis is FiO_2).

The variation in adjustments between the modes shows that while there were many more adjustments in the automated mode, the number of manual over-rides in the automated mode was very low (maximum two per patient). Nursing staff reported that the automated adjustments were often far greater in number and magnitude than they would normally perform, but also that the adjustments were rapid. The tendency of the algorithm to alternate between oversaturation and undersaturation may be due to excessive FiO_2 adjustments, and 'damping' of this response may be required to further improve the stability of oxygen control. It is not known whether this degree and/or rate of fluctuation of FiO_2 is clinically important at tissue level, given that these episodes were brief and overall babies spent more time adhering to the target SpO_2 range.

In our study, babies spent more time with FiO_2=21% in the automated arm, and while the minimisation of unnecessary oxygen exposure is desirable, the stability of the median FiO_2 may also be an important consideration. Larger studies are thus needed to examine clinical outcomes affected by oxygen exposure, such as Retinopathy of Prematurity (ROP)[16] , Bronchopulmonary Dysplasia (BPD)[17] and neurodevelopmental outcomes[1] in the context of automated oxygen control. In the meantime, we cannot necessarily assume that improved targeting will lead to a reduction in these morbidities.

Our study was a pragmatic study of oxygen requirement and adjustment, so that we enrolled a heterogeneous group of preterm babies who were sufficiently clinically stable to be enrolled, but who required oxygen and needed regular adjustments to their FiO_2 when in the manual mode to stay in SpO_2 target range. The cause of their oxygen requirement was not recorded. With a cross-over design we considered that the stability of the baby would not be expected to vary greatly over the 48 hours' study period and that babies with episodes of apparent intrapulmonary shunting should not be excluded from the study provided they remained on HF.

On a cautionary note, automated control of oxygen has the potential to reduce the reliability of desaturation episodes as a clinical diagnostic indicator of the baby's stability. If automated devices are to be routinely introduced, alternative indicators of clinical deterioration must be robust to prevent false reassurance provided by a stable SpO_2.

CONCLUSION

The IntellO_2 device in automated control mode maintained the babies' SpO_2 in the target SpO_2 range significantly more effectively than manual control, and reduced the duration of hypoxic and hyperoxic episodes. A larger study is needed to determine if this better targeting would improve clinical outcomes.

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Competing interests PRR and KI have received travel support and undertaken consulting work for Vapotherm. TLM, LIV and GCD were employees of Vapotherm during the study. NH and CCR have no declarations.

Patient consent Written parental consent was obtained for every study participant

Ethics approval MHRA Devices Division and Research Ethics Committee (London-Chelsea 16/LO/1272).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We are happy to share aggregated data; individual data are not made available to ensure that individual subjects cannot be identified.

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