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Salverda, H.H.; Cramer, S.J.E.; Witlox, R.S.G.M.; Gale, T.J.; Dargaville, P.A.; Pauws, S.C.; Pas, A.B. te

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Hylke H Salverda ,[1] Sophie J E Cramer,[1] Ruben S G M Witlox,[1] Timothy J Gale,[2] Peter A Dargaville,[3,4] Steffen C Pauws,[1,5] Arjan B te Pas[1]

[1]Willem-Alexander Children's Hospital, Department of Paediatrics, Division of Neonatology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
[2]School of Engineering and ICT, University of Tasmania, Hobart, Tasmania, Australia
[3]Department of Pediatrics, Royal Hobart Hospital, Hobart, Tasmania, Australia
[4]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[5]Tilburg Center for Cognition and Communication, Tilburg University, Tilburg, Noord-Brabant, The Netherlands

Correspondence to
Dr Hylke H Salverda, Neonatology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands; H.H.Salverda@lumc.nl

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ABSTRACT

Objective To compare the effect of two different automated oxygen control devices on target range (TR) time and occurrence of hypoxaemic and hyperoxaemic episodes.

Design Randomised cross-over study.

Setting Tertiary level neonatal unit in the Netherlands.

Patients Preterm infants (n=15) born between 24+0 and 29+6 days of gestation, receiving invasive or non-invasive respiratory support with oxygen saturation (SpO_2) TR of 91%–95%. Median gestational age 26 weeks and 4 days (IQR 25 weeks 3 days–27 weeks 6 days) and postnatal age 19 (IQR 17–24) days.

Interventions Inspired oxygen concentration was titrated by the OxyGenie controller (SLE6000 ventilator) and the $CLiO_2$ controller (AVEA ventilator) for 24 hours each, in a random sequence, with the respiratory support mode kept constant.

Main outcome measures Time spent within set SpO_2 TR (91%–95% with supplemental oxygen and 91%–100% without supplemental oxygen).

Results Time spent within the SpO_2 TR was higher during OxyGenie control (80.2 (72.6–82.4)% vs 68.5 (56.7–79.3)%, p<0.005). Less time was spent above TR while in supplemental oxygen (6.3 (5.1–9.9)% vs 15.9 (11.5–30.7)%, p<0.005) but more time spent below TR during OxyGenie control (14.7 (11.8%–17.2%) vs 9.3 (8.2–12.6)%, p<0.05). There was no significant difference in time with SpO_2 <80% (0.5 (0.1–1.0)% vs 0.2 (0.1–0.4)%, p=0.061). Long-lasting SpO_2 deviations occurred less frequently during OxyGenie control.

Conclusions The OxyGenie control algorithm was more effective in keeping the oxygen saturation within TR and preventing hyperoxaemia and equally effective in preventing hypoxaemia (SpO_2 <80%), although at the cost of a small increase in mild hypoxaemia.

Trial registry number NCT03877198

What is already known on this topic?

- Automated oxygen controllers, including the ones used in this study, increase time spent within the oxygen saturation target range compared with manual control.
- Hypoxaemia and hyperoxaemia have been linked to morbidity and mortality in preterm infants.

What this study adds?

- The OxyGenie controller was more effective in keeping the oxygen saturation within SpO_2 target range than the $CLiO_2$ controller.
- With OxyGenie, less time was spent above target range, fewer hypoxaemic and hyperoxaemic episodes occurred, although with a small increase in time below target range.
- Algorithm design influences how effective SpO_2 targeting will be.

INTRODUCTION

Oxygen therapy for preterm infants with respiratory insufficiency aims to prevent or moderate the effects of hypoxaemia on the central nervous system, lungs and other organs. Conversely, the immaturity of the premature infant's lungs, eyes and antioxidant system renders them vulnerable to exposure to supplemental oxygen, and hyperoxaemia has been linked to the development of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP).[1 2]

Mindful of these morbidities, the inhaled fraction of oxygen (FiO_2) is titrated manually, based on oxygen saturation (SpO_2) readings derived from transcutaneous oximetry. Current guidelines recommend a lower limit for the SpO_2 target range (TR) of at least 90% for the preterm infant,[3] based on the recent NeOProM meta-analysis of individual patient data from large randomised controlled trials.[4] These trials highlighted the potential impact of hypoxaemia and hyperoxaemia on preterm infants, with the lower TR (85%–89%) associated with an increased risk of mortality and necrotising enterocolitis and the higher TR (91%–95%) with an increased rate of ROP.

While the need to target an SpO_2 range is widely accepted, data from cohort studies and randomised controlled trials point to the difficulty of SpO_2 targeting by manual oxygen titration,[5–10] with most studies reporting SpO_2 values to be within the TR less than 50% of the time. Although bedside staff adjust the fraction of inspired oxygen (FiO_2) relatively frequently to maintain SpO_2 within TR, their workload limits time availability and makes it difficult to tailor FiO_2 continuously to the infant's need. This is compounded by the neonatal oxygenation physiology being unstable and non-linear with

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significant time delay between FiO_2 adjustment and when SpO_2 reaches a new stable level.[11]

Given both the importance and difficulty of SpO_2 targeting, automated oxygen control (AOC) is a logical improvement on current practice. In essence, the concept is of an SpO_2 input to a device holding a set of computational instructions (an algorithm), which then gives an output, an updated value for FiO_2. Studies comparing automated oxygen titration systems with manual titration, conducted over short periods (2–24 hours per epoch), have demonstrated an absolute increase in the proportion of time spent with SpO_2 within TR varying between 8% and 31%.[12–23] A single study conducted in our institution has examined the effect of implementation of AOC as standard of care, finding a 14% increase in TR time in the postimplementation cohort, mostly related to a decrease in time above TR.[24]

Although several devices offering AOC are now commercially available and used in neonatal intensive care units (NICUs), comparisons between them are lacking. The NICU of the Leiden University Medical Center (LUMC) implemented AOC with the $CLiO_2$ algorithm (Vyaire, Yorba Linda, California, USA) with the AVEA ventilator as routine care in August 2015. We recently replaced the AVEA ventilators with SLE6000 ventilators (SLE Limited, South Croydon, UK), which have the VDL 1.1 algorithm for AOC embedded as the "OxyGenie" option.[17 25] This provided the unique setting where caregivers were competent to work with both ventilators, thus making feasible a safe comparison between the two oxygen controllers.

Based on described differences in the function of algorithms developed for AOC, it is likely that they will exhibit differences in performance.[17 25] We recently observed that the $CLiO_2$ algorithm was effective mostly in decreasing time above TR,[24] whereas the first clinical study using OxyGenie reported a decrease in both time under and above TR and a virtual elimination of longer episodes outside the TR.[23] We therefore hypothesised that the OxyGenie may be more effective than $CLiO_2$ in maintaining SpO_2 within the desired TR in preterm infants receiving respiratory support.

METHODS

Study setting

We performed a randomised crossover trial in the NICU of the LUMC, a tertiary level neonatal unit with 25 NICU beds and 850 intensive care admissions per year. The Dutch Central Committee on Research Involving Human Subjects approved the study. Written informed parental consent was acquired prior to participation of each infant in the study.

Study population

Preterm infants born between from 24 weeks and up to and including 29 weeks of gestation who were receiving invasive mechanical ventilation or non-invasive respiratory support were assessed for eligibility . Initially, infants were considered eligible if they required supplemental oxygen with an FiO_2 ≥0.25 at the time of enrolment and for at least 18 hours of the preceding 24 hours, but as the study progressed an alternative FiO_2 eligibility criterion was added (FiO_2 coefficient of variation ≥0.1 in the preceding 24 hours) to improve recruitment rate. Infants were excluded in case of major congenital anomalies or acute instability.

Automated oxygen control algorithms

The $CLiO_2$ algorithm embedded in the AVEA ventilator is a hybrid rule-based adaptive controller. It makes initial FiO_2 adjustments that are proportional to the difference between the measured SpO_2 and the limits of the SpO_2 TR. Subsequent adjustments also take into account this difference, as well as the SpO_2 trend and basal oxygen requirement, the *baseFiO*$_2$. The *baseFiO*$_2$ is periodically updated by interrogation of 5 min of recent SpO_2 and FiO_2 data where specific conditions are met, averaged along with the current *baseFiO*$_2$ value.[26]

The OxyGenie algorithm embedded in the SLE6000 ventilator is an adaptive proportional-integral-derivative (PID) controller. The P, I and D terms each have separate coefficients, and in each case are adjusted from raw values to better suit the physiology of a neonate and account for the limitations of pulse oximetry. The basal FiO_2, referred to as *Reference FiO*$_2$, is calculated every 30 min using 60 min of preceding FiO_2 and SpO_2 values.

Study procedures

A crossover design was used to study each infant on the same respiratory support mode. Infants received two consecutive study periods of 24 hours each, one with oxygen therapy under the control of the $CLiO_2$ algorithm and the other with the OxyGenie algorithm, in random sequence. Web-based randomisation by Castor EDC (Castor, Amsterdam, The Netherlands) was used, stratified by mode of respiratory support (invasive or non-invasive) using variable (4, 6) block sizes. After the first study period, the alternative ventilator was substituted, and a washout period of 1 hour was applied before data recording restarted to prevent a carryover bias. The study was completed when AOC with each device had been applied for 24 hours, with standard respiratory management thereafter resuming. The SpO_2 TR for both study periods was 91%–95%.

No other extra interventions were given. Infants did receive all standard treatments, and ventilation settings were at the discretion of the caregiver.

Data collection and analysis

Baseline characteristics were noted for each infant, including details on respiratory support and clinical state. The primary outcome was the proportion of time spent within the SpO_2 TR (91%–95% with supplemental oxygen or 91%–100% without supplemental oxygen). SpO_2 and intended FiO_2 values were recorded each second from the data port or display of the ventilator under investigation. Secondary outcomes included: proportion of time in various degrees of hypoxaemia (SpO_2 <80%, SpO_2 80%–84%, SpO_2 85%–90%, SpO_2 ≤90%) and hyperoxaemia (SpO_2 >95%, SpO_2 96%–98% and SpO_2 >98% while receiving supplemental oxygen); SpO_2 and FiO_2 coefficient of variation; frequency of 30 and 60 s episodes in hypoxaemia and hyperoxaemia; bradycardic episodes (heart rate <100 beats per minute for ≥10 consecutive seconds); frequency of FiO_2 adjustments, both manual and automatic and average oxygen exposure.

Continuous data are represented as median (IQR) or mean±SD as appropriate, with standard tests for normality. Time within particular SpO_2 ranges was collated for each infant individually and expressed as proportion of usable recorded time. Differences in time in TR and other outcomes were assessed with the Wilcoxon matched-pairs test. The intention-to-treat principle was applied. Statistical analyses were performed by an analysist blinded to allocation using R V.3.4.4 (R Core Team (2016). R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, URL: https://www.R-project.org/).

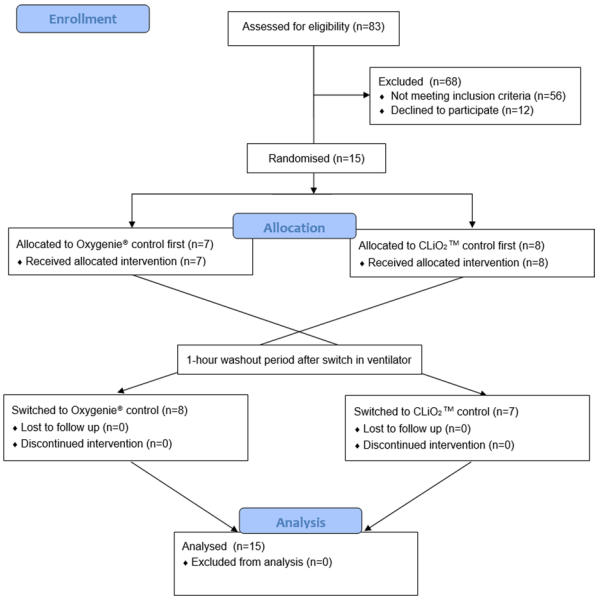

Figure 1 CONSORT flow diagram.

Sample size calculation was based around data from previous studies of the two automated control algorithms. In a study using the $CLiO_2$ in Leiden in preterm infants the proportion of time in the SpO_2 TR was 60.4% (±15.6%).[24] In the first clinical study of the OxyGenie algorithm TR time was 78% (±15%). We considered a difference of 5% TR time a clinically relevant difference. For a two-sided paired statistical test, 44 infants would be needed assuming a SD of 10% for a power of 90% and an alpha of 0.05. Because a non-parametric test would be used in the analysis, we made a 15% addition to the sample size, as described by Lehmann,[27] requiring a total of 50 participants.

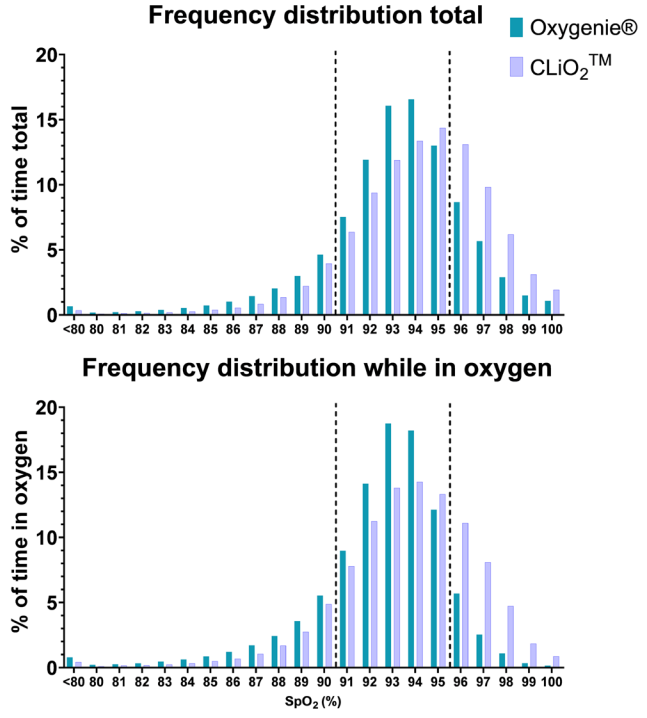

Figure 2 SpO_2 histograms. Pooled time spent per SpO_2 value as proportion of total usable time, while receiving supplemental oxygen and ambient air (total) or while only receiving supplemental oxygen. Dashed lines represent the limits of the SpO_2 target range.

Table 1 Baseline characteristics

Characteristic n=15	Definition	Statistics	Results
Gestational age	weeks, days	Median (IQR)	26.4 (25.3–27.6)
Birth weight	g	Median (IQR)	945 (740–1120)
Postnatal age	days	Median (IQR)	19 (17–24)
Gender	Female/male	n	4/11
Ventilation mode	Invasive ventilation/CPAP	n	2/13
Average FiO_2 over 24 hours prestudy	Fraction	Median (IQR)	0.26 (0.24–0.29)
Weight at study entry	g	Median (IQR)	1197 (1021–1300)
Allocation	Oxygenie first/ $CLiO_2$ first	n	7/8

CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen.

Early termination

Just prior to study commencement, the SLE6000 ventilator was deployed as the standard device for neonatal respiratory support at LUMC. The AVEA ventilators were thereafter only used when an infant was included in the study. Based on historical data, we anticipated to complete recruitment in a year, which was also considered the maximum time competence of medical staff in working with both ventilators could be guaranteed. However, the recruitment rate was slower than expected and to ensure patient safety and an unbiased comparison of both oxygen control with the two ventilators the trial was terminated after a 12-month recruiting period.

RESULTS

The study ran from February 2019 to February 2020, during which consent was sought from 27 parent couples of which 15 agreed to participate (figure 1). All participating infants (n=15, baseline characteristics table 1) completed the crossover comparison. In one infant, the second study period (OxyGenie control) was halted after 18 hours to allow treating clinicians to switch from continuous positive airway pressure to nasal high flow in response to nasal pressure areas. All study periods were included in the analysis. The total duration of recordings was 23 hours and 19 min (22:52–23:30) during OxyGenie control and 23 hours and 51 min (23:49–23:56) with the $CLiO_2$ controller. A total of 2.9% (2.1%–5.0%) and 0.3% (0.2%–0.6%) of the time the SpO_2 signal was missing, respectively.

Histograms of pooled SpO_2 data from the two automated control periods are shown in figure 2, demonstrating a narrower SpO_2 distribution and a lower median SpO_2 during OxyGenie control resulting in a higher proportion of time within the SpO_2 TR. On per patient analysis, for the study primary outcome, there was a 11.7% increase in time within the SpO_2 TR during oxygen control with the OxyGenie algorithm when compared with the $CLiO_2$ device (table 2). Twelve infants spent more time in TR with OxyGenie control and three with $CLiO_2$ control (figure 3). During the OxyGenie period, less time was spent above the TR while in supplemental oxygen, but more time spent below TR. SpO_2 values <80% were very infrequent throughout the study, and the time with SpO_2 <80% did not differ between control devices. The coefficient of variation for SpO_2 was similar for both devices (3.3% (2.6%–4.0%) vs 3.2% (3.0%–3.4%), p=0.82).

Table 2 Proportions of time within SpO_2 ranges

	Oxygenie	$CLiO_2$	P value*
Time SpO_2 within target range†	80.2 (72.6–82.4)%	68.5 (56.7–79.3)%	0.005
Time SpO_2 below target range	14.7 (11.8–17.2)%	9.3 (8.2–12.6)%	0.020
Time SpO_2 above target range‡	6.3 (5.1–9.9)%	15.9 (11.5–30.7)%	0.001
SpO_2 85%–90%	12.6 (10.9–13.1)%	8.5 (7.6–11.0)%	0.020
SpO_2 80%–84%	1.2 (0.7–3.0)%	0.8 (0.5–0.9)%	0.003
SpO_2 <80%	0.5 (0.1–1.0)%	0.2 (0.1–0.4)%	0.061
SpO_2 96%–98% while $FiO_2 \geq 0.22$	6.1 (5.0–9.5)%	15.5 (10.9–27.4)%	0.001
SpO_2 >98% while $FiO_2 \geq 0.22$	0.2 (0.1–0.4)%	1.4 (0.4–3.7)%	0.001

Data in median (IQR)
*Wilcoxon matched pairs test.
†91% ≤SpO_2 ≤95% or SpO_2 ≥96% while FiO_2=0.21.
‡SpO_2 ≥96% while FiO_2 ≥0.22.

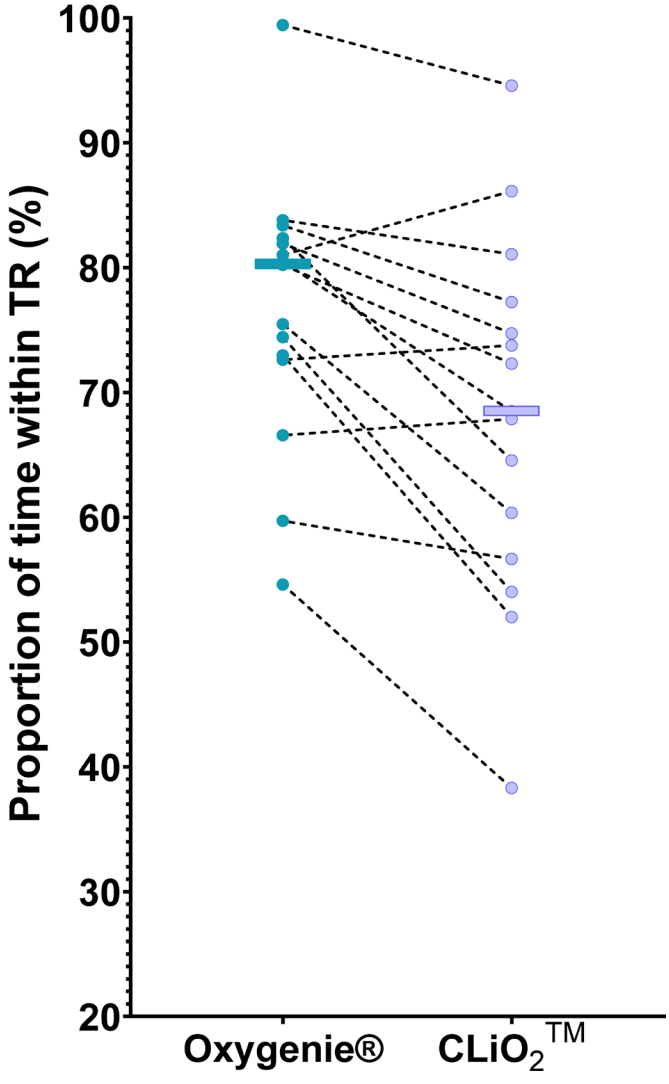

Figure 3 Comparison of OxyGenie control with $CLiO_2$ control. Individual paired values of proportion of time within TR while on OxyGenie control and while on $CLiO_2$ control. Horizontal bar=median. Within TR=91%–95% with supplemental oxygen or 91%–100% without supplemental oxygen. TR, target range.

There was a decrease in frequency of both hypoxaemic and hyperoxaemic episodes during OxyGenie control (table 3). Bradycardic episodes (<100 bpm for ≥10 s) were rare in both epochs and were not different (0.3 (0.1–0.6) vs 0.2 (0.0–0.5) per hour, p=0.22).

OxyGenie adjusted FiO_2 about 10 times more frequently than the $CLiO_2$ device (1155 (1044–1255) vs 194 (178–205) adjustments/hour, p=0.001). The average delivered FiO_2 was similar during both study periods (0.27+−0.05 vs 0.26 +−0.08, p=0.56). FiO_2 was more variable when titrated by the OxyGenie algorithm (coefficient of variation 19.5% (15.2%–25.0%) vs 13.3% (12.8%–19.0%), p=0.015). During OxyGenie control, manual overrides of the AOC were made only in one individual subject (four adjustments) versus nine individuals (16 adjustments) with manual overrides during the period of $CLiO_2$ oxygen control.

DISCUSSION

In this randomised controlled crossover study, automated titration of inspired oxygen concentration using the OxyGenie controller significantly increased the time spent within the SpO_2 TR when compared with the $CLiO_2$ controller. The difference in controller function was reflected in the SpO_2 histogram, with a more balanced distribution of SpO_2 values within and around the TR during OxyGenie control. This resulted in significantly less time spent above the TR, and fewer hyperoxaemic episodes, although at the cost of a small increase in time spent with SpO_2 values below TR. The greater time with SpO2 in the range 80%–90% with OxyGenie compared with $CLiO_2$ control was not accompanied by an increase in the frequency of hypoxic episodes, which were, indeed, significantly fewer during OxyGenie control. These results suggest that algorithm design, and in particular algorithm responsiveness, plays an important role in how successful SpO_2 targeting will be with a given oxygen control device.

This is the first study to compare two different ventilators incorporating AOC algorithms head-to-head. Although earlier studies have individually compared the algorithms in question to manual oxygen titration,[15–20 23 24] heterogeneity between the studies has precluded drawing inferences about their function relative to each other. Our findings in relation to proportion of time within TR were similar to previous studies, implying that the SpO_2 targeting results achieved by controllers in our study were representative of their overall performance. Compared with the TR time of 80% in this study, other studies of OxyGenie control have demonstrated TR times of 81%[23] and 88%.[28] For $CLiO_2$ (69% TR time in this study), other studies have shown TR time of 40%,[15] 58%,[16] 62%,[18] 76%,[19] 73%[20] and 62%[24]).

The study was terminated before reaching the predetermined sample size of 50 infants. The deployment of the SLE6000 ventilator at LUMC had an impact on numbers of eligible infants by virtue of (1) the option of nasal high flow (not available with the AVEA ventilator) being taken up at an early juncture in many preterm infants, precluding involvement in the study and (2) fewer infants spending >18 of the preceding 24 hours with an FiO_2 ≥0.25, in part attributable to the progressive approach to weaning FiO_2 inherent in OxyGenie control. As a result, the recruitment rate was lower than expected. To prevent a loss of competence in handling the AVEA ventilator, potentially introducing a bias into the study, we decided to terminate the study prematurely. Truncated clinical studies can lead to overexaggerated observed effects.[29 30] For our study, this would mean that the observed benefit for the OxyGenie controller in comparison

Table 3 Hypoxaemic and hyperoxaemic episodes

	30 s episodes/6 hours			60 s episodes/6 hours		
	Oxygenie	$CLiO_2$	P value*	Oxygenie	$CLiO_2$	P value*
SpO_2 <85%	0.5 (0.2–1.1)	0.8 (0.5–1.7)	0.022	0 (0–0.24)	0.2 (0–0.8)	0.027
SpO_2 <80%	0 (0–0)	0.2 (0–0.5)	0.011	0 (0–0)	0 (0–0)	0.257
SpO_2 >95%†	4.4 (2.6–10.7)	37.3 (15.8–54.3)	0.009	0.8 (0.4–2.6)	14.6 (5.5–22.8)	0.008
SpO_2 >98%†	0.2 (0–0.8)	6.3 (1.7–13.6)	0.004	0 (0–0.2)	1.7 (0.5–5.3)	0.002

Data in median (IQR).
*Wilcoxon matched pairs test.
†While $FiO_2 \geq 0.22$.

to $CLiO_2$ controller may overestimate the true benefit. However, if we had planned for an interim analysis to decide for stopping the trial after 15 patients, we would have surpassed both the Pocock and O'Brien-Fleming boundary criteria for clearly showing evidence of benefit for the OxyGenie controller. For a single interim analysis, Pocock recommends a p-threshold of 0.0294[31] and O'Brien-Fleming recommends a more conservative 0.0054 p-threshold[32] to control for type I error due to repeated testing. The apparent benefit of OxyGenie is also demonstrated by a 11.7% improvement which is more than twice the clinically relevant difference of 5% for which the current study was powered.

There was an imbalance between the two oxygen control devices in the proportion of missing values. Both algorithms use a built-in Masimo pulse oximeter with similar algorithms making it unlikely that the actual reliability of pulse oximeter measurement was different between ventilators. But, to ensure a prompt response to TR deviations, OxyGenie uses a 2–4 s averaging time whereas $CLiO_2$ uses an 8 s averaging time. This could lead to more missing signal, as shorter averaging times are inherently more susceptible to disturbances. Furthermore, although the same SET technology is used, manufacturers are free to choose the signal quality threshold below which SpO_2 is reported as missing. It seems likely that the handling of the SpO_2 signal within the SLE6000 is more conservative in this respect. Because the proportion of missing signal was still relatively low in both oxygen control periods, its effect on the outcomes of this study is likely to have been modest.

This study compared two ventilators rather than purely the AOC algorithms. It is possible that ventilator mechanics also played a role in the effectiveness of oxygen control as well as other aspects of ventilator function including the circuit flow characteristics.[33] However, this was a pragmatic choice as license agreements precluded us from implementing two algorithms in one ventilator.

Contrary to our hypothesis, the benefit of an increase in SpO_2 TR time with OxyGenie control was gained with a lesser occurrence of hyperoxaemia, at the cost of a minor increase in time spent with SpO_2 80%–90%. Although at first glance it appears there is a trade-off between hyperoxaemia and hypoxaemia, the reduction in hypoxaemic episodes with OxyGenie control suggests that hypoxaemia is resolved more quickly. This is in line with the clinical observation of caregivers, who reported that OxyGenie responded more rapidly to SpO_2 deviations into hypoxaemia than $CLiO_2$. Compared with other studies, time with SpO_2 <80% was modest with both controllers. For the OxyGenie controller, it was 0.5% in our study vs 0%[23] previously; for the $CLiO_2$ controller, it was 0.2% whereas other studies reported 9.8%,[15] 1.2% and 0.8%,[18] 3.1%,[19] 1.3%[20] and 0.9%.[24]

The increase in time spent under TR could be due to a lower median SpO_2 during OxyGenie control (93% vs 94%) on the steeper part of the oxygen-dissociation curve. The higher median SpO_2 during $CLiO_2$ control could be because, according to the patent, an SpO_2 of 94% is targeted while in TR and the FiO_2 is rarely titrated below the *BaseFiO*$_2$.[26]

Even though the benefit of AOC on SpO_2 TR time is well-established, the effect on clinical outcome is still unknown. The effect of SpO_2 targeting within different ranges on clinical outcome was demonstrated by the NeOPRoM trials,[4] and a range of studies have evidenced the harmful effects of hypoxaemia and hyperoxaemia (and episodes thereof),[34–39] both of which are affected by AOC. We would maintain that when searching for clinical effect of AOC, it is important to use an algorithm that most successfully avoids and mitigates SpO_2 deviations, because the effect on clinical outcomes may be modest and in some cases may be difficult to detect given their relatively low incidence.

Finally, low compliance in TR adherence such as reported in the NeOPRoM trials[4] could be improved on by using AOC. For the best differentiation between treatment groups, it is important to have a controller that best targets the predefined ranges.

CONCLUSION

In this study, the OxyGenie controller was more effective in keeping the oxygen saturation within TR and preventing hyperoxaemia, and just as effective in preventing hypoxaemia (SpO_2 <80%), although at the cost of a small increase with SpO_2 80%–90%.

Twitter Arjan B te Pas @None

Contributors HHS: co-conceived the study (with ABtP) conducted the study, compiled, analysed and interpreted the data (with SCP), co-wrote the first draft of the manuscript and approved the final version of the manuscript. SJEC: reviewed and edited the manuscript, conducted the study and approved the final version of the manuscript. RSGMW: reviewed and edited the manuscript, acquired data and approved the final version of the manuscript. TJG: reviewed and edited the manuscript, interpreted the data and approved the final version of the manuscript. PAD: interpreted the data, reviewed and edited the manuscript and approved the final version of the manuscript. SCP: reviewed and edited the manuscript, performed the analysis and interpretation of the data and approved the final version of the manuscript. ABtP: co-conceived the study, oversaw the study conduct, interpreted the data, cowrote the first draft of the manuscript and approved the final version.

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Data availability statement Data are available on reasonable request.

ORCID iD

Hylke H Salverda http://orcid.org/0000-0001-9355-5993

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