Outcomes after automated oxygen control for preterm infants

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What is known about this topic

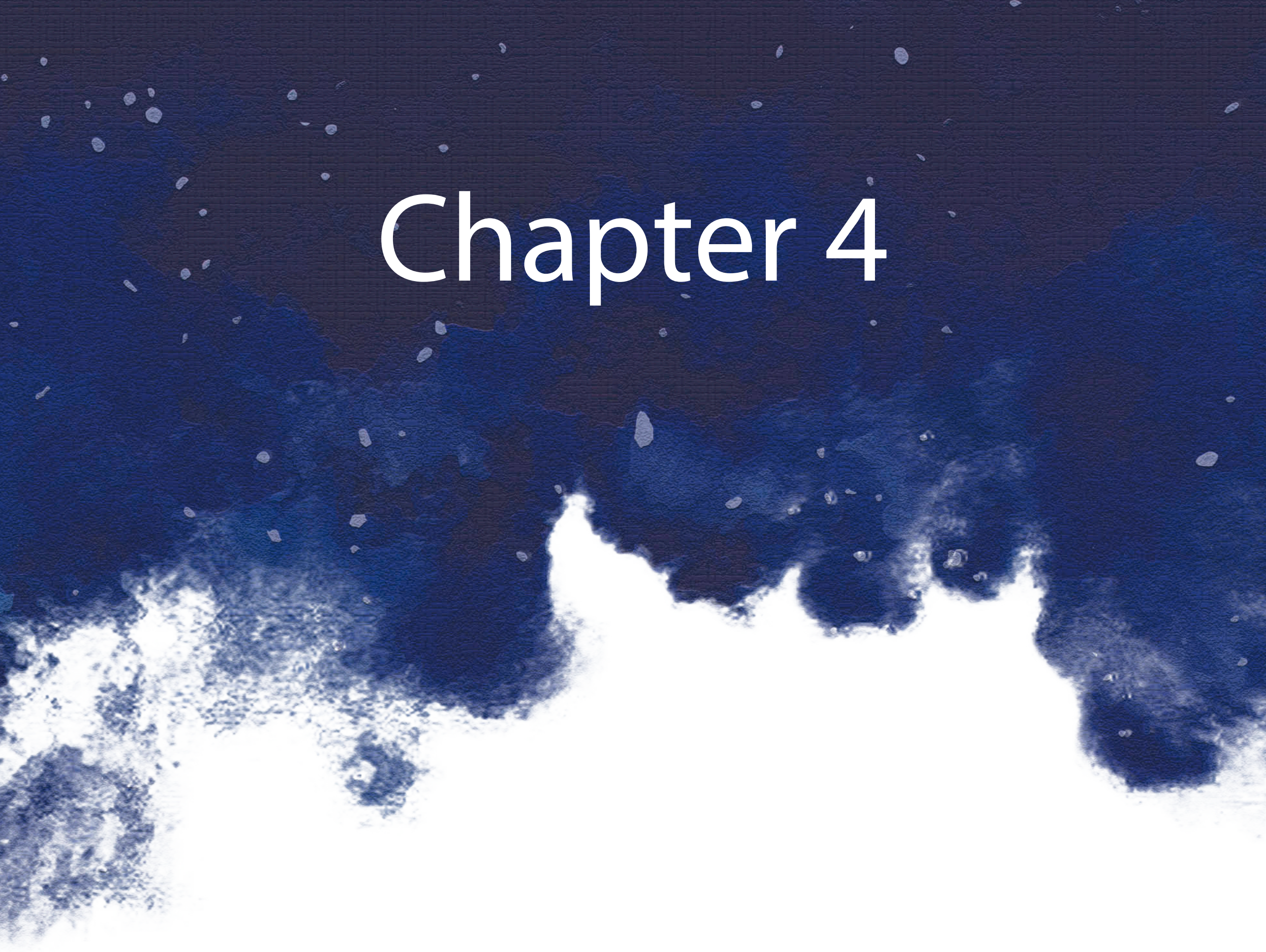
- Automated oxygen control has been proven to increase time spent within SpO_2 target range when compared with manual titration in cross-over studies lasting a maximum of 24 hours.
- Algorithm choice may influence how successful titration will be, but comparisons of algorithms head-to-head are scarce.
- A preterm infant's response to an adjustment in FiO_2 may change during the course of the admission as respiratory distress syndrome progresses.

What this study adds

- Automated oxygen titration by the OxyGenie algorithm was associated with better oxygen saturation targeting during the entire admission while given oxygen when compared to titration by the $CLiO_2$ algorithm.
- This was accompanied by less time spent in hypoxia and hyperoxia for preterm infants supported by the OxyGenie algorithm.
- Including episodes where no supplemental oxygen is administered reduces the effect size.

How this study might affect research, practice or policy

- Choice of automated oxygen controller is associated with how successful oxygenation targeting will be during the entire admission.
- When researching a long period of oxygen titration focus should lie on phases of respiratory instability and/or when supplemental oxygen is administered.



Chapter 4

Comparison of two automated oxygen controllers in oxygen targeting in preterm infants during admission – an observational study

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Abstract

Objective To compare the effect of two different automated oxygen control devices in preterm infants on time spent in different oxygen saturation (SpO2) ranges during their entire stay in the NICU.

Design Retrospective cohort study of prospectively collected data.

Setting Tertiary level neonatal unit in the Netherlands.

Patients Preterm infants (OxyGenie 75 infants, CLiO2 111 infants) born at 24-29 weeks gestation receiving at least 72 hours of respiratory support between October 2015 and November 2020.

Interventions Inspired oxygen concentration was titrated by the OxyGenie controller (SLE6000 ventilator) between February 2019 and November 2020 and the CLiO2 controller (AVEA ventilator) between October 2015 and December 2018 as standard of care.

Main outcome measures Time spent within SpO2 target range (TR, 91-95% for either epoch) and other SpO2 ranges.

Results Time spent within the SpO2 TR when receiving supplemental oxygen was higher during OxyGenie control (median 71.5 [IQR 64.6–77.0]% vs 51.3 [47.3–58.5]%, $p<0.001$). Infants under OxyGenie control spent less time in hypoxic and hyperoxic ranges (SpO2<80%: 0.7 [0.4–1.4]% vs 1.2 [0.7–2.3]%, $p<0.001$; SpO2 >98%: 1.0 [0.5-2.4]% vs 4.0 [2.0-7.9]%, $p<0.001$). Both groups received a similar FiO2 (29.5 [28.0 – 33.2]% vs 29.6 [27.7-32.1]%, p=non significant)

Conclusions Oxygen saturation targeting was better in the OxyGenie epoch in preterm infants, with less time in hypoxic and hyperoxic SpO2 ranges during their stay in NICU.

Keywords: Hypoxemia; hyperoxia; closed-loop; algorithm; neonate

Introduction

Caregivers in the Neonatal Intensive Care Unit (NICU) must continuously maintain a fragile balance between administering too much and too little supplemental oxygen to preterm infants to prevent neonatal morbidity and mortality. Several neonatal morbidities have been linked to a disturbance in this balance, with intermittent hypoxia being associated with retinopathy of prematurity,[1] neurodevelopmental impairment and death,[2] and hyperoxia long known to be causative of retinopathy of prematurity.[3]

Maintaining the balance involves titration of the inspired fraction of oxygen (FiO_2). When done manually this often leads to an achieved time within the oxygen saturation (SpO_2) target range of 50% or less.[4] Automated targeting of SpO_2 by a device titrating FiO_2 can increase the time that preterm infants spend within the target range.[5, 6] In general, automated oxygen titration entails a computer program that automatically adjusts the FiO_2 based on the measured SpO_2. The magnitude of the FiO_2 adjustment is usually determined by several factors, such as the currently administered FiO_2 and the difference between the measured SpO_2 and the intended SpO_2. Several of these devices are available commercially.[7-13] The function of all of these devices has been examined in cross-over studies lasting 24 hours or less per arm, and has proved superior to manual titration, but head-to-head comparisons of devices are scarce.[12, 14]

Algorithm choice may influence how successful titration will be.[15] We recently demonstrated the OxyGenie controller (SLE Limited, South Croydon, UK) to be more effective in maintaining SpO_2 within target range than the $CLiO_2$ controller (Vyaire, Yorba Linda, California, USA) in a randomised 48 hour crossover study.[14] In this trial, infants were studied at a median postnatal age of 19 days at which time the lung disease and response to changes in FiO_2 may not be representative of each phase of admission.

To date no studies have compared automated oxygen controllers head-to-head over long periods of time. In our centre, we are in the unique position of having used two different automated oxygen controllers as standard of care for a total of 6 years, making a comparison between these two controllers feasible. We used the AVEA ventilators with the $CLiO_2$ automated oxygen control (AOC) algorithm integrated for over three years (since August 2015), after which the ventilators were replaced for SLE6000 ventilators with OxyGenie AOC algorithm in November 2018. In this study we compared the effectiveness of these controllers in very preterm infants receiving AOC as standard of care by either the $CLiO_2$ or the OxyGenie controller during their entire admission. Considering the results from our cross-over study[14], we hypothesized that OxyGenie is more effective in maintaining SpO_2 within the target range during respiratory support of preterm infants.

Methods

Study setting

We retrospectively retrieved prospectively collected data of all patients born at 24-29 weeks gestation, admitted to the NICU of the LUMC between October 2015 and November 2020. Our centre is a tertiary-level perinatal centre in Leiden, the Netherlands, and we have an average of 100 infants born under 30 weeks of gestation per annum. In the Netherlands, no ethical approval is required for anonymised studies with patient data collected for standard care. The Medical Ethical Review Committee of Leiden Den Haag Delft provided a statement of no objection for obtaining and publishing the anonymised data.

Infants were excluded if they: were admitted >24 hours after birth, had major congenital abnormalities, or received less than 72 hours of respiratory support. A minimum of 72 hours was chosen to exclude unrepresentative extreme scores from infants transferred within days after birth with little respiratory support, or infants who died shortly after birth. In both situations the impact of automated oxygen titration would likely be negligible. The AVEA cohort consisted of infants admitted between October 18th 2015 (three months after implementation of $CLiO_2$ into standard care) to December 1st 2018, the SLE cohort consisted of infants born between February 1st 2019 and November 1st 2020, allowing for a wash-out period of two months.

Respiratory support

Both the OxyGenie and the $CLiO_2$ algorithm change the FiO_2 automatically according to the measured SpO_2, where generally larger deviations from the SpO_2 target range lead to larger changes in FiO_2. Both are adaptive in the sense that when a patients' average supplemental oxygen requirement is higher, adjustments in FiO_2 will also be larger. One difference lies in the exact way the adjustment in FiO_2 is calculated: both OxyGenie and $CLiO_2$ base the magnitude of adjustment on how far out of the target range the current SpO_2 is, and the trajectory of recent values, but OxyGenie also takes past values into account (by addition of an integral term, the sum of past differences between desired and measured SpO_2). More detail on the function of these algorithms can be found elsewhere.[15]

Modes of respiratory support used during both epochs were invasive mechanical ventilation (volume targeted, high frequency oscillation (HFO)), continuous positive airway pressure or non-invasive positive pressure ventilation, high flow nasal cannula (HFNC), and low flow. The SLE6000 supports all these modes, whereas during the AVEA epoch HFNC was administered via the Optiflow system (Fisher & Paykel Healthcare, Auckland, New Zealand) and HFO via a Sensormedics 3100 A ventilator (Vyaire, Yorba Linda, California, USA). Both the AVEA and the SLE6000 ventilator have Masimo SET technology on board to measure SpO_2, but with different fixed settings for averaging time during AOC (SLE6000: 2-4 seconds, AVEA: 8 seconds). Automated oxygen control was not available during HFNC or HFO support during the AVEA period, and these periods were excluded in the primary analysis for both epochs.

The SpO_2 target range during $CLiO_2$ control was 90%-95%, which needed to be changed to 91%-95% on introduction of the SLE6000 as this is a pre-set target range. For the purpose of the primary analysis the target range was considered to be 91%-95%. Local protocol is to disable automated oxygen control when infants received no supplemental oxygen while saturating >98% for more than 30 minutes or a few days prior to transfer to a different hospital. Our local protocol is to set SpO_2 alarm limits to 88%-98%.

Data collection and analysis

Patient characteristics and vital parameters up to a postmenstrual age of 30 weeks were sourced from our patient data management system (PDMS Metavision; IMDsoft, Tel Aviv, Israel). The instantaneous SpO_2 and FiO_2 were stored once per minute, we recently demonstrated that there were no significant differences when using one-per-minute vs. one-per-second data for descriptive statistics such as time within target range.[16] Small for gestational age was defined as a birth weight under p10 in the Hoftiezer curves.[17]

There is an incongruency in the incoming FiO_2 values between the SLE6000 and AVEA. In case of the SLE6000, data forwarded to our patient data management system consists of measured FiO_2 by the SLE6000's oxygen cell. For this cell the accuracy is 3%.[18] In some cases this leads to situations where the ventilator is providing no supplemental oxygen, or 21% of oxygen, while the recorded FiO_2 is 23%. Contrary to the SLE6000, AVEA's recorded values for FiO_2 are based on the intended, or set, FiO_2 rather than the measured FiO_2. Therefore we chose to define room air, or no supplemental oxygen, as any FiO_2 value of 23% or lower.

For the primary analysis, recording periods where no supplemental oxygen was administered were removed. Infants receiving less than 72 h of supplemental oxygen were excluded from the primary analysis. We then calculated the proportion of time within SpO_2 target range (SpO_2 91%-95%), proportions of time in various degrees of hypoxia (SpO_2 <80%, SpO_2 80%-84%, SpO_2 85-90%, SpO_2 ≤90%) or hyperoxia (SpO_2 >95%, SpO_2 96%-98%, and SpO_2 >98, and average FiO_2. These outcomes were calculated overall and per day. Finally, we calculated the proportion of time within target range per week of postmenstrual age. For the secondary analysis we calculated the overall outcomes using all periods of respiratory support (i.e. also room air) from infants receiving at least 72 hours of respiratory support.

Continuous data is represented as median (IQR) or mean ±SD as appropriate, with standard tests for normality. Differences in time in target range and other outcomes were assessed with the Kruskal-Wallis test. Statistical analyses were performed using MATLAB (Matlab R2020b; The MathWorks Inc., Natick, Massachusetts, USA).

Results

Patient characteristics

In the study period 449 preterm infants born at 24-29 weeks of gestation were admitted to the LUMC NICU within 24 hours after birth, 154 in the OxyGenie epoch and 295 in the $CLiO_2$ epoch. Of these, 146 infants remained in the OxyGenie epoch and 269 infants in the $CLiO_2$ epoch after exclusion of infants receiving less than 72 hours of respiratory support. The primary analysis, including only infants receiving at least 72 h supplemental oxygen, involved 75 infants in the OxyGenie epoch and 111 infants in the $CLiO_2$ epoch. There were no significant differences in any of the baseline characteristics for the primary outcome population (Table 1). The median recording length of vital parameters was 336 hours [IQR 186 – 598] in the OxyGenie epoch and 398 [IQR 165 – 693] in the $CLiO_2$ epoch (p = not significant (ns)).

Table 1. Baseline characteristics of recordings >72 hours while supplemental oxygen administered

Patient characteristics **n = 186**	**Oxygenie** **n=75**	**CLiO$_2$** **n=111**	**p value***
Gestational age in weeks $^{\text{days}}$, median [IQR]	27^0 [25^3 – 27^5)	26^6 [25^4 – 28^0]	n.s.
Birth weight in grams, mean (SD)	934 (239)	901 (215)	n.s.
Small for gestational age, n (%)	8 (10.7)	8 (7.2)	n.s.
Males, n (%)	42 (56.0)	52 (46.8)	n.s.
Antenatal corticosteroids, n (%)	66 (88.0)	94 (84.7)	n.s.
Caesarean delivery, n (%)	36 (48.0)	63 (56.8)	n.s.
Multiple pregnancy, n (%)	26 (34.7)	42 (37.8)	n.s.
Recording length in hours, median [IQR]	336 [186 – 598]	398 [165 – 693]	n.s.

*FiO$_2$, fraction of inspired oxygen; CPAP, continuous positive airway pressure; *Mann-Whitney U test, independent T-test or chi-square test as appropriate*

Baseline characteristics for the secondary analysis population also did not differ between epochs (Table 2). Median recording length of vital parameters was 490 hours [IQR 350 – 747] in the OxyGenie epoch and 520 [IQR 321 – 751] in the CLiO$_2$ epoch (p = ns).

Table 2. Baseline characteristics of all recordings >72 hours, including room air episodes

Patient characteristics **N = 415**	**Oxygenie** **N=146**	**CLiO$_2$** **N=269**	**p value***
Gestational age in weeks $^{\text{days}}$, median [IQR]	28^0 [26^6 – 29^0]	28^1 [26^6 – 28^6]	n.s.
Birth weight in grams, mean (SD)	1038 (270)	1050 (250)	n.s.
Small for gestational age, n (%)	16 (11.0)	21 (7.8)	n.s.
Males, n (%)	137 (50.9)	80 (54.8)	n.s.
Antenatal corticosteroids, n (%)	133 (91.1)	236 (87.7)	n.s.
Caesarean delivery, n (%)	74 (50.7)	148 (55.0)	n.s.
Multiple pregnancy, n (%)	55 (37.7)	93 (34.6)	n.s.
Recording length in hours, median [IQR]	490 [350 – 747]	520 [321 – 751]	n.s.

*FiO$_2$, fraction of inspired oxygen; CPAP, continuous positive airway pressure; *Mann-Whitney U test, independent T-test or chi-square test as appropriate*

Time within SpO_2 ranges

In the primary analysis where episodes of room air were excluded, infants in the OxyGenie epoch spent 71.5 [64.6 – 77.0] % of the time within target range of 91%-95% versus 51.3 [47.3 – 58.5] % in the $CLiO_2$ epoch ($p < 0.001$, Table 3). This was mainly attributable to less time above the target range in the OxyGenie epoch (OxyGenie 11.5 [8.7 – 15.8] %, $CLiO_2$ 23.9 [16.3 – 32.1] %, $p < 0.001$), and to a lesser extent to a reduction in time under the target range (OxyGenie 16.1 [12.6 – 19.2], $CLiO_2$ 22.0 [18.2 – 26.0], $p < 0.001$). Oxygen saturations under 80% were measured 0.7 [0.4 – 1.4] % of the time with OxyGenie and 1.2 [0.7 – 2.3] % of the time with $CLiO_2$ ($p < 0.001$); oxygen saturations above 98% were measured 1.0 [0.5 – 2.4] % of the time with OxyGenie and 4.0 [2.0 – 7.9] % of the time with $CLiO_2$ ($p < 0.001$). The average FiO_2 was not significantly different.

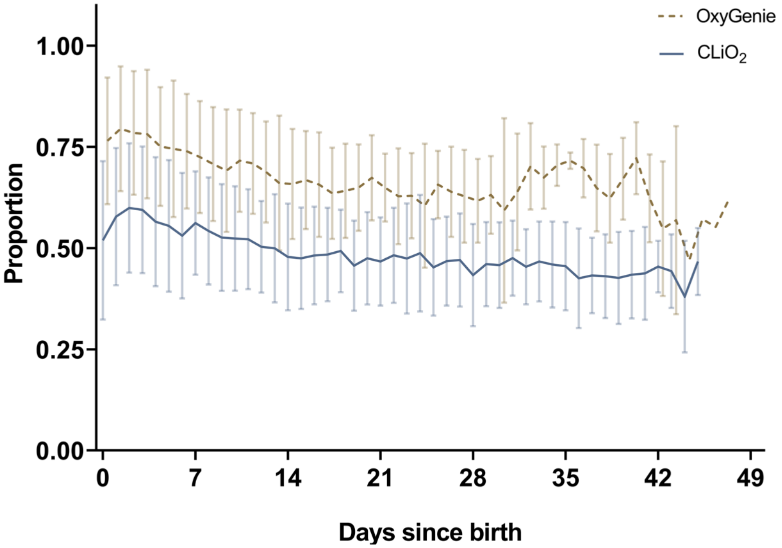
Table 3. Recordings >72 hours while supplemental oxygen administered, excluding episodes in room air

Outcome		**Oxygenie N=75**	**$CLiO_2$ N=111**	**p value***
Time SpO_2 in target range†	%	71.5 [64.6 – 77.0]	51.3 [47.3 – 58.5]	<0.001
Time SpO_2 < target range	%	16.1 [12.6 – 19.2]	22.0 [18.2 – 26.0]	<0.001
Time SpO_2 > target range	%	11.5 [8.7 – 15.8]	23.9 [16.3 – 32.1]	<0.001
SpO_2 85% - 89%	%	8.3 [6.5 – 9.9]	11.6 [9.5 – 14.1]	<0.001
SpO_2 80% - 84%	%	1.7 [1.0 – 2.3]	2.9 [1.8 – 3.8]	<0.001
SpO_2 < 80%	%	0.7 [0.4 – 1.4]	1.2 [0.7 – 2.3]	<0.001
SpO_2 96% - 98%	%	10.5 [7.7 – 13.7]	19.3 [14.3 – 24.1]	<0.001
SpO_2 > 98%	%	1.0 [0.5 – 2.4]	4.0 [2.0 – 7.9]	<0.001
Average FiO_2§	%	29.5 [28.0 – 33.2]	29.6 [27.7 – 32.1]	n.s.

*Data in median [IQR]; * Kruskal-Wallis test; † 91% <= SpO_2 <= 95%; § Average FiO_2 is based on measured FiO_2 for OxyGenie and on intended/set FiO_2 for $CLiO_2$*

In figure 1A, 1C and 1D the average proportion of time within the SpO_2 different ranges (SpO_2 91-95%, SpO_2 <80%, SpO_2 >98% respectively) can be viewed per day since birth, which shows a decline in proportion with increasing age. When set against the postmenstrual age this decline is less apparent in the OxyGenie group (Figure 1B). The average FiO_2 excluding room air (Figure 2) has a similar course for both epochs, although around the age of 30 days and 50 days there are fewer infants contributing to the data leading to a higher standard deviation and differences between controllers.

A Proportion of time within SpO_2 target range - excluding room air



B Proportion within SpO_2 target range - per week - excluding room air

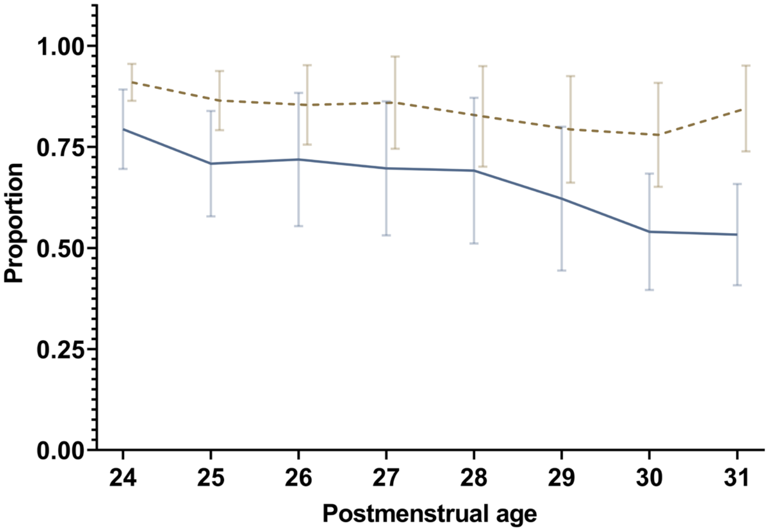


Figure 1A-B. *Proportion of time spent within different SpO_2 ranges excluding periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$. (A): Proportion of time within the 91%-95% range plotted against postnatal age. (B): Proportion of time within the 91%-95% range plotted against postmenstrual age. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$.*

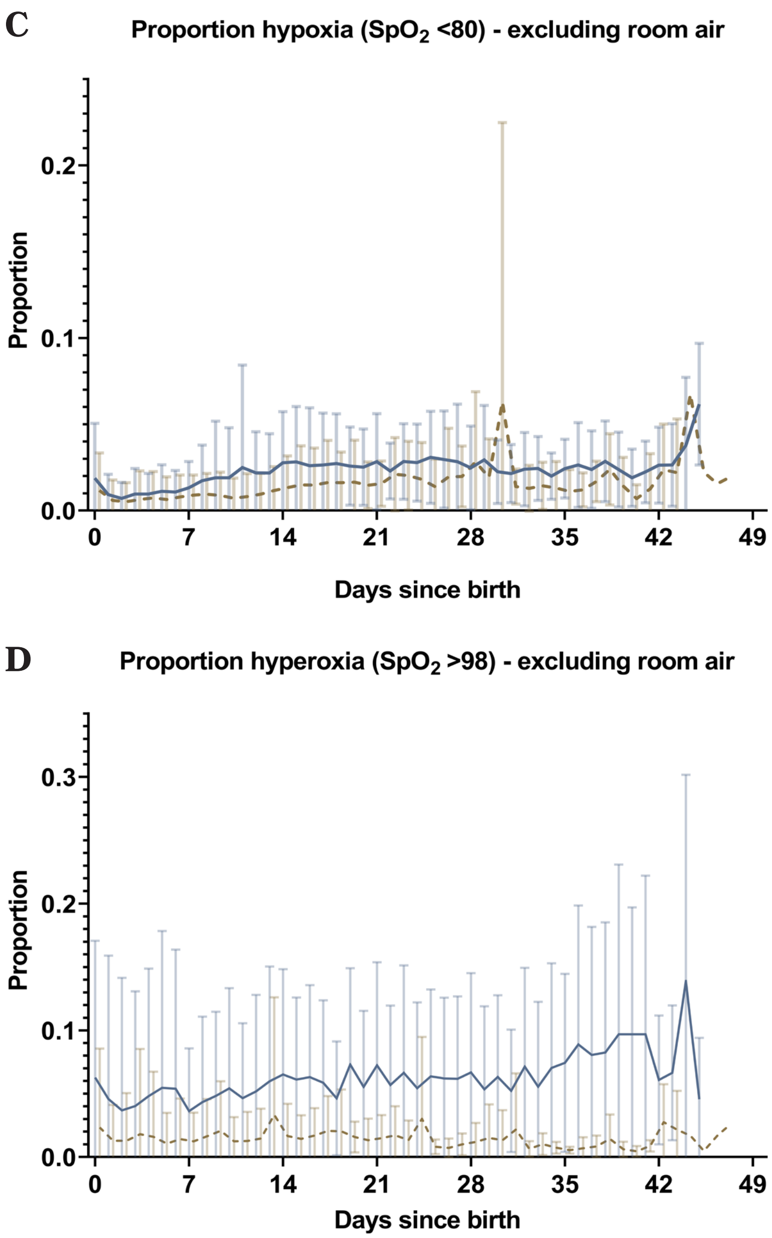


Figure 1C-D. *Proportion of time spent within different SpO_2 ranges excluding periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$. (C): Proportion of time in hypoxia (SpO_2 <80%) against postnatal age. (D): Proportion of time in hyperoxia (SpO_2 >98%) against postnatal age. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$.*

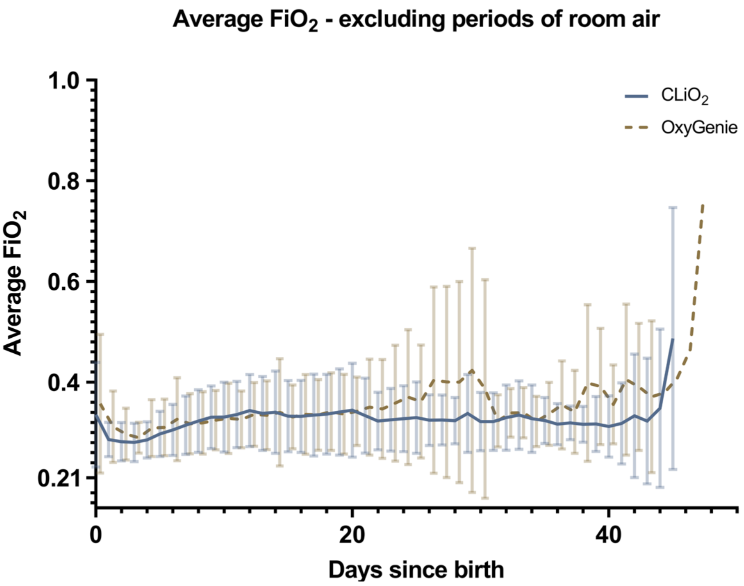


Figure 2. *Average FiO_2 excluding values FiO_2<0.24 plotted against postnatal age.*

In the secondary analysis infants on OxyGenie spent 92.5 [91.8 – 97.2] % of the time within target range versus 90.2 [75.2 – 96.0] % of the time for infants on $CLiO_2$ (p = 0.005, Table 4, Figure 3A per day, Figure 3B per week postmenstrual age). Contrary to the primary analysis, the differences were mainly attributed to a reduction in time under the target range, which was 5.0 [2.2 – 5.9] % in OxyGenie and 6.8 [3.3 – 13.6] % in $CLiO_2$ (p = 0.003). Time above target range was similar (OxyGenie 2.0 [0.7 – 5.9], $CLiO_2$ 2.5 [0.4 – 10.9, p = ns). Major SpO_2 deviations were less common in OxyGenie (SpO_2 <80%: OxyGenie 0.2 [0.1 – 0.5] %, $CLiO_2$ 0.3 [0.2 – 0.8] %, p <0.001, Figure 3C; SpO_2 >98%: OxyGenie 0.2 [0.1 – 0.6] %, $CLiO_2$ 0.4 [0.1 – 1.7] %, p <0.001, Figure 3D). The recorded average FiO_2 was lower in the $CLiO_2$ group (OxyGenie 23.0 [21.8 – 25.8] %, $CLiO_2$ 21.8 [21.1 – 24.8] %, p < 0.001).

Table 4. Recordings >72 hours, including episodes in room air

Outcome		**Oxygenie** **n=146**	**$CLiO_2$** **n=269**	**p value***
Time SpO_2 within target range†	%	92.5 [81.8 – 97.2]	90.2 [75.2 – 96.0]	0.005
Time SpO_2 below target range	%	5.0 [2.2 – 10.6]	6.8 [3.3 – 13.6]	0.003
Time SpO_2 above target range‡	%	2.0 [0.7 – 5.9]	2.5 [0.4 – 10.9]	n.s.
SpO_2 85% - 89%	%	2.7 [1.1 – 5.3]	3.7 [1.6 – 7.6]	0.002
SpO_2 80% - 84%	%	0.4 [0.2 – 1.2]	0.8 [0.3 – 1.7]	<0.001
SpO_2 < 80%	%	0.2 [0.1 – 0.5]	0.3 [0.2 – 0.8]	<0.001
SpO_2 96% - 98% while FiO_2 >= 0.24	%	1.7 [0.6 – 5.2]	1.9 [0.3 – 9.0]	n.s.
SpO_2 > 98% while FiO_2 >= 0.24	%	0.2 [0.1 – 0.6]	0.4 [0.1 – 1.7]	<0.001
Average FiO_2§	%	23.0 [21.8 – 25.8]	21.8 [21.1 – 24.8]	<0.001

*Data in median (IQR). * Kruskal-Wallis test. † 91% <= SpO_2 <= 95% or SpO_2 >= 96% while FiO_2 <= 0.23. ‡ SpO_2 >= 96% while FiO_2 >= 0.24 § Average FiO_2 is based on measured FiO_2 for OxyGenie and on intended/set FiO_2 for $CLiO_2$*

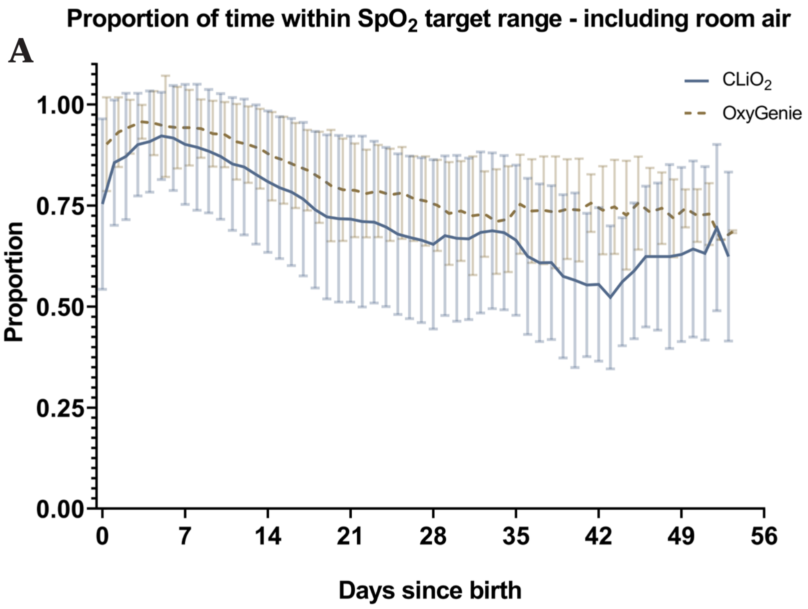


Figure 3A. *Proportion of time spent within different SpO_2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: $CLiO_2$*

(A): Proportion of time within the 91%-95% range plotted against postnatal age.

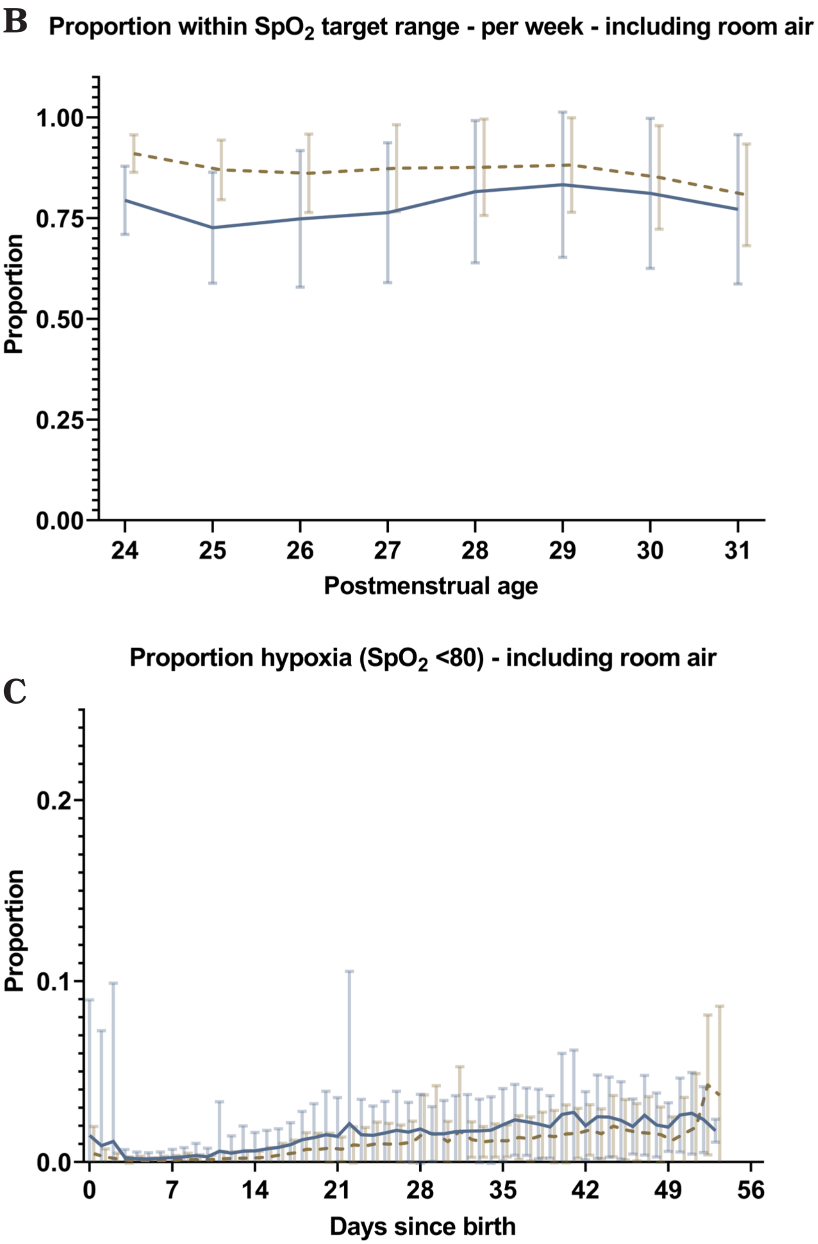


Figure 3B-C. *Proportion of time spent within different SpO2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: CLiO*$_2$

(B): Proportion of time within the 91%-95% range plotted against postmenstrual age. (C): Proportion of time in hypoxia (SpO$_2$ *<80%) against postnatal age.*

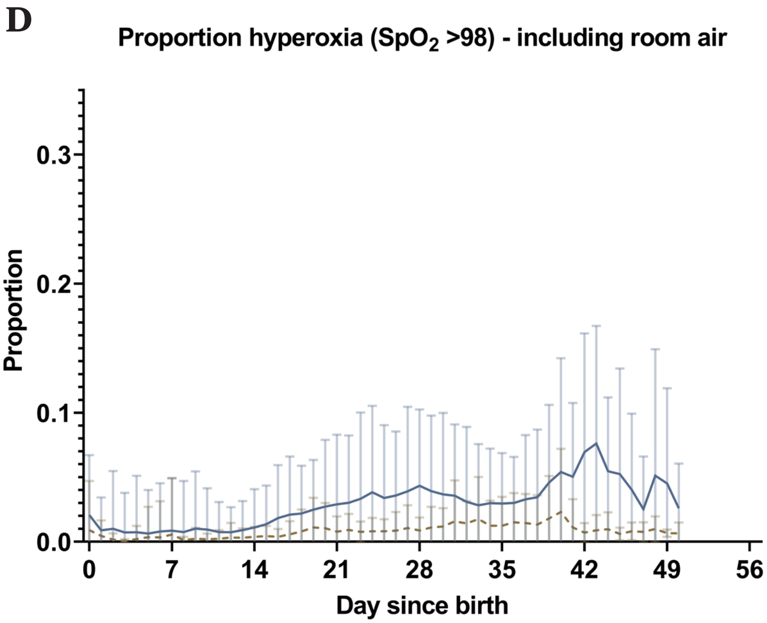


Figure 3D. *Proportion of time spent within different SpO2 ranges including periods where no supplemental oxygen is administered. Dashed brown line: OxyGenie control, solid blue line: CLiO*$_2$

(D): Proportion of time in hyperoxia (SpO$_2$ *>98%) against postnatal age.*

Discussion

In this study preterm infants receiving OxyGenie automated oxygen control during their stay in the NICU spent significantly more time within the target range than infants receiving CLiO$_2$ automated oxygen control. This improvement was driven by less time spent in all hypoxic and hyperoxic ranges during supplemental oxygen therapy, and this improvement remained during all postnatal and postmenstrual ages. No differences were found in average inspired oxygen when supplemental oxygen is administered. The effect size reduced when episodes without supplemental oxygen were also included, but the superiority of OxyGenie was nevertheless still present. These results suggest that the conclusion from our randomised cross-over study[14] – the choice of oxygen control device determines how successful SpO$_2$ targeting will be – holds true for the entire stay in the NICU.

This is the first study to describe the proportions of time within certain oxygen saturation ranges during different phases of a preterm infants' stay in the NICU. In only one study automated oxygen control during the entire stay was researched.

In this study, where $CLiO_2$ was compared with manual titration, results for hypoxia were similar to our $CLiO_2$ study group, but hyperoxia was slightly lower and time within target range higher. Contrary to the randomised cross-over study[14] comparing OxyGenie with $CLiO_2$ for 24-hours periods, OxyGenie control was associated with less time under target range. This may be due to the differences in analysis (in the crossover study periods without supplemental oxygen were included, and intended FiO_2 rather than measured FiO_2 was collected for both devices).

Our choice in definition of room air may have influenced the results. Unfortunately, it was not possible to retrieve the intended FiO_2 for the OxyGenie group, as this is not routinely collected, and measured FiO_2 was not routinely collected for the $CLiO_2$ group. To increase the validity of the comparison between AVEA and SLE6000, we excluded periods where the inspired oxygen concentration was 23% or lower, reducing the penalty the SLE6000 would inherently receive for measuring more than 21% of inspired oxygen while no supplemental oxygen is given. As such, only less stable episodes with higher risk of hyperoxaemia are studied.

Unique in this study is that we investigated the relation between postnatal age and time spent within certain oxygen saturation ranges. As demonstrated in our secondary analysis, comparing achieved target range time can be heavily influenced by the relatively stable respiratory period that usually occurs after a postmenstrual age of 30 weeks. Compared with our primary analysis, one can ascertain all results are diluted by this stable period of near-100% time within target range. Better oxygenation results will not be achieved in phases where infants receive no supplemental oxygen because they are adequately saturated. Indeed, the benefit of an AOC will be modest as then its only role is to respond to intermittent hypoxia, triggered by apnoea or other destabilising events. The focus for research concerning the entire admission should lie on phases where the infant exhibits less respiratory stability and receives supplemental oxygen.

Decisions made during the analysis may have influenced the results, but were important to maintain generalisability. Periods in the AVEA epoch where HFO or HFNC was the mode of respiratory support were excluded in the oxygen-only analysis, as there was no automated oxygen control available during these times. Furthermore, we excluded infants requiring less than 72 hours of respiratory support because their data could skew the results while their outcome was based on relatively little information and not representative for the average very preterm infant: they were either too stable and saturated fully immediately or they died soon after birth, which is highly unlikely to be related to choice of oxygen control device.

The difference in algorithm design and responsiveness could explain our results. Exact and clear information on the workings of the $CLiO_2$ algorithm is limited, but one can infer from the patent document that only in few cases FiO_2 is titrated below the *BaseFiO2* – a derivative of the average oxygen requirement. This could mean $CLiO_2$ is slower to reduce the administered oxygen, possibly leading to more hyperoxia. Moreover, a longer averaging time employed by $CLiO_2$ leads to a delay in pickup of deviations, which is further amplified by a timeout applied to prevent responding to erroneous SpO_2 values.[19] These choices in algorithm design can lead to tardier algorithm responsiveness, and may therefore lead to less time within the oxygen saturation target range.

Combined with the results of our cross-over study, the results show that choice of oxygen control device influences achieved time within oxygen saturation ranges in the preterm infant. Although choice of AOC may not be of great impact on achieved target range time over the entire course of admission, it could very well be that most morbidity finds its genesis in the periods of respiratory instability, during which a prominent difference is noted between the two AOC algorithms. A higher incidence of retinopathy of prematurity has been found to be associated with intermittent hypoxia[1] as well as hyperoxia, both of which occur more often in periods of respiratory instability. Indeed, in a matched cohort study we reported a lower incidence of retinopathy of prematurity for infants under OxyGenie automated oxygen control.[20] Although causality cannot be inferred from these results, all results of our recent studies are pointing in the same direction.

Conclusion

In this cohort study of oxygen saturation data collected from entire NICU admissions, the epoch in which OxyGenie was used was associated with significantly better oxygen saturation targeting when compared to the period in which CLiO$_2$ was used. This was accompanied by less time spent in hypoxia and hyperoxia for infants supported by OxyGenie automated oxygen control.

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