Outcomes after automated oxygen control for preterm infants

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What is already known on this topic

- Automated oxygen controllers, including the ones utilised 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 period in which the OxyGenie controller was used was associated with less laser treatment for ROP and a shorter stay in the NICU.
- The period in which the OxyGenie controller was used was associated with less invasive ventilation and continuous positive airway pressure days

How this study might affect research, practice or policy

- The currently used definition for BPD may not be suitable when automated oxygen control is used
- Choice of automated oxygen controller may be associated with clinical outcome, a large randomised trial is warranted.

Chapter 8

Clinical outcomes of preterm infants while using automated controllers during standard care: comparison of cohorts with different automated titration strategies

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Abstract

Objective To compare short-term clinical outcome after using two different automated oxygen controllers (OxyGenie and $CLiO_2$)

Design Propensity score matched retrospective observational study

Setting Tertiary level neonatal unit in the Netherlands

Patients Preterm infants (OxyGenie n=121, $CLiO_2$ n=121) born between 24+0-29+6 weeks of gestation. Median [IQR] gestational age in the OxyGenie cohort was 28+3 [26+3.5–29+0] versus 27+5 [26+5–28+3] in the $CLiO_2$ cohort, respectively 42% and 46% of infants were male and mean (SD) birth weight was 1034 (266) grams vs 1022 (242) grams.

Interventions Inspired oxygen was titrated by OxyGenie (SLE6000) or $CLiO_2$ (AVEA) during respiratory support.

Main outcome measures Mortality, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis.

Results Fewer infants in the OxyGenie group received laser coagulation for ROP (1 infant vs 10; risk ratio 0.1 (95%-CI 0.0 – 0.7); p=0.008), and infants stayed shorter in the NICU (28 [15-42] vs 40 [25-61] days; median difference 13.5 days (95%-CI 8.5 – 19.5); p<0.001). Infants in the OxyGenie group had fewer days on continuous positive airway pressure (8.4 [4.8-19.8] days vs. 16.7 [6.3-31.1]; p<0.001) and significantly shorter number of days on invasive ventilation (0 [0-4.2] days vs. 2.1 [0-8.4]; p=0.012). There were no statistically significant differences in all other morbidities.

Conclusions In this propensity score matched retrospective study, the OxyGenie epoch was associated with less morbidity when compared to the $CLiO_2$ epoch. There were significantly fewer infants that received treatment for ROP, received less intensive respiratory support and, although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. A larger study will have to replicate these findings.

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

Introduction

Very preterm infants undergo a long undertaking from birth to discharge from the hospital out of which few arise unscathed. Four in ten of these infants experience a serious adverse outcome such as in-hospital mortality, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) requiring treatment or severe neurologic injury.[1] As demonstrated by a post-hoc analysis of the data from NeOProM meta-analysis, these outcomes are likely to be at least partly affected by the degree of success in targeting a specific oxygen saturation range (SpO_2 TR).[2, 3]

Targeting the SpO_2 TR is done by carefully titrating the administered supplemental oxygen during respiratory support, either manually by bedside staff or by an automated oxygen controller (AOC). There are currently multiple systems commercially available for automated titration of the supplied oxygen.[4-9] All current evidence points towards more overall success for AOCs on achieved time within the SpO_2 TR.

However, the available controllers employ different algorithms[10] and it is unclear which of these algorithms lead to better long and short-term outcome. The one algorithm X may on average keep oxygen saturation higher and have fewer desaturations at the cost of more hyperoxaemia; whereas the other algorithm Y may adhere better to the defined oxygen saturation limits at the cost of more short but frequent desaturations. Both the increase in hyperoxaemia with algorithm X could increase the risk for ROP, and the higher incidence of intermittent hypoxaemia with algorithm Y could yield similar effects.[11, 12] Furthermore, the amplitude of SpO_2 fluctuations and the duration of the episodes will most likely also be a factor of influence. Both factors can be influenced by choice of algorithm, for example by algorithm design, pulse-oximeter settings and choice of SpO_2 TR. A similar conundrum may exist for BPD, neurodevelopmental and other long-term outcomes.[12, 13] Studies comparing these clinical outcomes for different AOCs are lacking.

Two controllers employing distinctly different algorithms, the $CLiO_2$ algorithm implemented in the AVEA ventilator (Vyaire, Yorba Linda, California, USA) and the OxyGenie algorithm (VDL 1.1) embedded in the SLE6000 ventilator (SLE Limited, South Croydon, UK) were used in the neonatal unit of Leiden University Medical Center (LUMC). Both algorithms have been described in detail in a recent publication.[10] We recently demonstrated that the OxyGenie algorithm was more effective in keeping SpO_2 within the SpO_2 TR, preventing hyperoxaemia, and just as effective in preventing hypoxaemia. While using the $CLiO_2$ algorithm there was less time spent in the SpO_2 range of 80%-90%, possibly due to the lower median

SpO_2 during OxyGenie control (93% vs 94%) on the steeper part of the oxygen-haemoglobin dissociation curve. We hypothesized that these differences in achieved performance may affect short-term clinical outcome. Both systems have been used as standard of care for over a year in our unit, which prompted us to describe short-term clinical outcomes of preterm infants in a matched cohort study.

Methods

Study design

We performed a propensity score-matched observational study with electronic patient record data from the LUMC, a tertiary hospital with 25 Neonatal Intensive Care Unit (NICU) beds and around 100 admissions per annum of infants born under 30 weeks of gestation. The medical ethical research committee of Leiden Den Haag Delft provided a statement of no objection for obtaining and publishing the anonymised data. Protocol was filed under reference number G19.075.

To ensure equal distribution of patient characteristics that can confound with outcome we matched infants that received respiratory support from the SLE6000 ventilator, born in-hospital between November 1st 2018 and March 15th 2020 (OxyGenie cohort), to infants from a cohort supported by the AVEA ventilator born between 18th of October 2015 and the 31st of April 2018 ($CLiO_2$ cohort). We matched on sex, birthweight, and gestational age using propensity score matching with a match tolerance of 0.1. All infants were born at a gestational age 24+0 until 29+6 weeks. Infants with major congenital malformations were excluded.

Automated oxygen controllers

In August 2015 automated oxygen titration by the $CLiO_2$ algorithm was introduced as standard of care. The $CLiO_2$ algorithm was set to target an SpO_2 TR of 90%-95%. In November 2018 the AVEA ventilators were replaced with SLE6000 ventilators with the OxyGenie option for automated oxygen control. The OxyGenie uses a narrower SpO_2 TR of 91%-95%. The $CLiO_2$ algorithm is of a rule-based design. To determine a fraction of inspiratory oxygen (FiO_2) adjustment $CLiO_2$ incorporates the difference between the SpO_2 TR and the measured SpO_2, the severity of lung disease and the SpO_2 trend. The OxyGenie algorithm is an adaptive proportional-integral-derivative (PID) controller – also employed in automotive cruise-control and rockets – with several enhancements to account for the physiology of a neonate and account for the limitations of pulse oximetry.

Data collection and outcome measures

Patient records are kept digitally in our patient data management system (Metavision; IMDsoft, Tel Aviv, Israel). The following outcomes were noted from either these records or from the discharge papers from the regional hospital where the infant resided before being discharged home: mortality until one month after corrected term age, ROP, BPD, necrotising enterocolitis (NEC), culture proven sepsis, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), and length of NICU stay. The duration of respiratory therapy and supplemental oxygen (measured FiO_2 above 0.21) and the mean of inspiratory oxygen during the first week and entire admission were calculated from our patient data management system which routinely samples clinical parameters and ventilator settings once per minute. High flow nasal cannula (HFNC) was available in SLE6000, not in AVEA. The device we used for HFNC during the $CLiO_2$ period did not allow for automatic data storage or for automated oxygen titration. Therefore to minimise biased results, the duration of supplemental oxygen therapy was analysed both with and without periods of HFNC. The ophthalmologists in our hospital implemented the Early Treatment of Retinopathy of Prematurity study (ETROP) classification for findings of retinal examination in 2013 and ROP was defined according to this classification.[14, 15] Laser coagulation for treatment of severe ROP is first choice, anti-VEGF injections are not standard of care. When retinal findings were described otherwise, researcher *HHS* classified according to the ETROP criteria retrospectively, assisted by an ophthalmologist where necessary. An assessment for BPD was made at 36 weeks postmenstrual age classified as either none, mild, moderate-severe according to adapted criteria from the 2000-NICHD consensus. [16] We chose to combine the moderate and severe classifications as discharge papers from regional hospitals sometimes did not indicate which respiratory therapy was applied at what time. NEC was defined according to the modified Bell staging criteria[17], IVH was classified according to Papile's adapted classification [18, 19], PVL according to the de Vries' classification. [20]

Analysis

Data are presented as mean (SD), median [IQR] or (range), or number (percentage) as appropriate. Standard tests for normality (visual assessment, Kolmogorov-Smirnov, Shapiro-Wilk) were done. Statistical comparison was performed using a related-samples Wilcoxon signed rank test with Hodges-Lehman median difference confidence interval or related-samples McNemar test as appropriate. Outcomes with more than 2 categories were analysed using a Bhapkar test.[21] Risk ratios and confidence intervals were calculated according to the method described by Algresti

and Min[22] to retain the matching of the data. Statistical analyses were performed by IBM SPSS Statistics for Mac, version 25 (IBM, Armonk, New York, USA) and R 4.1.0 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Two-tailed P-values of <0.05 were considered statistically significant.

Results

158 infants were born between November 2018 - March 2020 of which 121 were eligible for inclusion in the OxyGenie cohort. These were then matched with infants born in the period October 2015 - April 2018 to form the control, or $CLiO_2$, cohort (n=121) (table 1). In the OxyGenie cohort 51 infants were male (42%), there was a median gestational age at birth of 28 weeks and 3 days [26 weeks and 3.5 days – 29 weeks] and a birth weight of 1034 (266) grams. In the $CLiO_2$ cohort there were 55 males (46%), there was a median gestational age of 27 weeks and 5 days [26 weeks and 5 days – 28 weeks and 3 days] and a birth weight of 1022 (242) grams. As our centre is a referral centre for foetal treatment we have a relatively large number of multiple pregnancy (45 in the OxyGenie cohort vs. 41 in the $CLiO_2$ cohort). There were no statistically significant differences between groups in beforementioned patient characteristics.

Table 1. Patient characteristics

Patient characteristics n = 242	**OxyGenie n = 121**	**$CLiO_2$ n = 121**	**p value***
Gestational age in weeks^{days}, median [IQR]	28^{3} [$26^{3.5}$ – 29]	27^{5} [26^{5} – 28^{3}]	0.09
Birth weight in grams, mean (SD)	1034 (266)	1022 (242)	0.60
Small for gestational age, n (%)	12 (10.1)	8 (6.6)	0.30
Males, n (%)	51 (42.1)	55 (45.5)	0.60
Antenatal corticosteroids, n (%)	107 (92.2)	106 (89.1)	0.50
Caesarean delivery, n (%)	64 (52.9)	66 (54.5)	0.90
Multiple pregnancy, n (%)	45 (37.2)	41 (33.9)	0.70
of which monochorionic twins, n (%)	22 (48.9)	26 (63.4)	
Perinatal asphyxia, n (%)	5 (4.1)	1 (0.8)	0.22
Apgar score at 5 minutes, median (range)	8 (0-10)	8 (2-10)	0.79

**Statistical analysis with related-samples Wilcoxon signed rank test or related-samples McNemar test as appropriate.*

Respiratory therapies

The OxyGenie cohort had significantly more time during which they received supplemental oxygen (table 2; 17.3 [6.0 – 31.1] days vs. 7.0 [1.1 – 26.1]; p = 0.045). High flow was not available in the AVEA ventilator, when excluding periods where infants where supported using high flow from the analysis there was a non-statistically significant difference (8.5 [2.8 - 22.6) days OxyGenie group vs. 7.0 [1.1 – 26.1] $CLiO_2$ group, p = 0.52). The mean inspired oxygen in the first week of life was similar in both groups (22.8 [21.8 – 25.0] % OxyGenie vs. 22.6 [21.4 – 24.8] %; p = 0.33), as was mean inspired oxygen during the entire stay (22.9 [21.8 – 25.3] % vs. 23.4 [21.6 – 27.0] %; p = 0.21). Infants in the OxyGenie cohort had fewer days of continuous positive airway pressure (CPAP; 8.4 [4.8 – 19.8] days vs. 16.7 [6.3 – 31.1] days; p < 0.001) and fewer days of invasive ventilation (0 [0 – 4.2] vs 2.1 [0 – 8.4]; p = 0.012) while the duration of nasal high flow was similar. There were no significant differences in number of infants who received inhaled nitric oxide, dexamethasone or surfactant.

Table 2. Respiratory therapies

	OxyGenie	**$CLiO_2$**	**p value***
Invasive ventilation days, median [IQR]	0 [0 – 4.2]	2.1 [0 – 8.4]	0.012
CPAP days, median [IQR]	8.4 [4.8 – 19.8]	16.7 [6.3 – 31.1]	<0.001
HFNC days, median [IQR]	10.0 [4.2 – 17.2]	8.2 [2.7 – 14.6]	0.20
Supplemental oxygen days, median [IQR]	17.3 [6.0 – 31.1]	7.0 [1.1 – 26.1]	0.045
excluding nasal high flow, median [IQR]	8.5 [2.8 – 22.6]	7.0 [1.1 – 26.1]	0.52
Mean inspired oxygen			
during first week, median [IQR]	22.8 [21.8 – 25.0]	22.6 [21.4 – 24.8]	0.33
entire admittance, median [IQR]	22.9 [21.8 – 25.3]	23.4 [21.6 – 27.0]	0.21
High frequency oscillation, n (%)	23 (19.0)	26 (21.5)	0.76
Inhaled nitric oxide, n (%)	13 (10.7)	15 (12.4)	0.85
Dexamethasone, n (%)	15 (12.4)	15 (12.4)	1.00
Surfactant, n (%)	67 (55.7)	69 (57.0)	0.89
via intubation, n (%)	28 (41.8)	38 (55.1)	0.32
via minimally invasive technique, n (%)	39 (58.2)	31 (44.9)	

*CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; Average inspired oxygen while on respiratory support. *Statistical analysis with related-samples Wilcoxon signed rank, Bhapkar or related-samples McNemar test as appropriate.*

Clinical outcomes

Fewer infants received laser coagulation for ROP in the OxyGenie cohort (table 3; 1 vs 10; Relative risk ratio (RR) 0.1, 95%-CI 0.0 to 0.7; p = 0.008), no infants were treated with anti-VEGF injections. There were no statistically significant differences in mortality (RR 2.3, 95%-CI 0.6 to 9.0), culture proven sepsis, BPD (RR 1.0 95%-CI 0.7 to 1.3), NEC (>stage 2A, RR 1.1 95%-CI 0.5 to 2.6), IVH (≥ stage 2, RR 1.5 95%-CI 0.8 – 2.7) and PVL (≥ stage 2, RR 0.3 95%-CI 0.0 – 2.2). Infants had a significantly shorter duration of stay in the NICU in the OxyGenie cohort (28 [15-42] vs. 40 [25-61] days; median difference 13.5 days (95%-CI 8.5 – 19.5); p < 0.001).

Table 3. Clinical outcomes

	OxyGenie	**CLiO$_2$**		**p value***
Died, n (%)	7 (5.8)	3 (2.5)	RR 2.3 (0.6 – 9.0)	0.34
Culture proven sepsis, n (%)	45 (37.2)	56 (46.3)	RR 1.2 (0.9 – 1.7)	0.18
Necrotising enterocolitis (> stage 2A), n (%)	9 (7.4)	8 (6.6)	RR 1.1 (0.5 – 2.6)	1.00
Retinopathy of prematurity				
ETROP 1, n (%)	5 (4.5)	13 (11.2)	RR 0.4 (0.2 – 1.1)	0.09
ETROP 2, n (%)	4 (3.6)	1 (0.9)	RR 4.0 (0.4 – 35.8)	
Received laser coagulation, n (%)	1 (0.9)	10 (8.6)	RR 0.1 (0.0 – 0.7)	0.008
Intraventricular haemorrhage (≥ stage 2), n (%)	27 (22.5)	18 (14.9)	RR 1.5 (0.8 – 2.7)	0.21
Periventricular leukomalacia (≥ stage 2), n (%)	1 (0.8)	4 (3.3)	RR 0.3 (0.0 – 2.2)	0.38
Days in NICU, median [IQR]	28 [15 – 42]	40 [25 – 61]	MD 13.5 (8.5 – 19.5)	<0.001
Bronchopulmonary dysplasia	52 (46.0)	58 (48.7)	RR 1.0 (0.7 – 1.3)	0.89
moderate/severe, n (%)	18 (34.6)	31 (53.4)	RR 0.7 (0.4 – 1.1)	0.18
mild, n (%)	34 (65.4)	27 (46.6)	RR 1.3 (0.8 – 1.9)	

*RR, relative risk; MD, median difference; ETROP, early treatment of retinopathy of prematurity; Necrotising enterocolitis according to modified Bell staging criteria; Intraventricular haemorrhage according to Papile's classification; Days on NICU until transfer to peripheral hospital or discharge; Bronchopulmonary dysplasia classification according to Dutch paediatric guidelines. *Statistical analysis with related-samples Wilcoxon signed rank, Bhapkar test or related-samples McNemar test as appropriate.*

Discussion

In this observational study infants in the OxyGenie group had less morbidity. Fewer infants needed laser coagulation for retinopathy of prematurity in the OxyGenie cohort when compared to the $CLiO_2$ cohort. On average, administered supplemental oxygen was of a modest proportion in both groups and with the exception of a shorter duration of continuous positive airway pressure and invasive mechanical ventilation, the durations on other modes of respiratory support were not significantly different. Infants in the OxyGenie cohort had a significantly shorter duration of stay in the NICU. Other short-term clinical outcomes were not significantly different between groups.

In a prior study we reported on the effect of AOC on clinical outcome during standard of care for preterm infants in which the AOC cohort consisted almost entirely of infants treated with the $CLiO_2$ algorithm.[23] In this larger cohort around 6% of infants needed laser coagulation for ROP, similar to what is previously reported (5.9%) in a cohort of over 154.000 very preterm infants. Contrary to our results, a recent study in the Netherlands reported an increase in treatment for ROP in the more recent epoch.[24] The prevalence was 2.3% in the most recent epoch, however the upper gestational age criterion was higher (i.e. 32 weeks).[1] These figures of prevalence, combined with the relatively modest cohort size, may be indicative that the prevalence of laser coagulation for retinopathy of prematurity in the $CLiO_2$ group may be an overestimation. Nevertheless, the occurrence of laser coagulation in the Oxygenie group was much lower than our prevalence during manual treatment.

A reduction in ROP when using OxyGenie could be plausible. In a randomised crossover trial comparing OxyGenie to $CLiO_2$ we reported significantly less time above target range, tighter target range adherence (i.e. less fluctuation of oxygenation) and less frequent and shorter episodes of both hypoxaemia and hyperoxaemia while using OxyGenie.[25] Hypoxaemia, hyperoxaemia, and fluctuation of oxygenation have all been associated with an increased rate of ROP.[11, 12, 26] Early after preterm birth, a varying oxygenation of the retina might lead to decreased retinal vascular growth and blood vessel loss, leaving the retina more susceptible to damage due to hypoxia. In a later phase, this increases the risk of uncontrolled neovascularisation and retinal detachment.[27] Although our randomised trial was limited to 48 hours per studied infant, there is no reason why those results cannot be generalised largely to the rest of the admission, as the postnatal age at study was variable. We did not have data on cardiotonic medication, the other risk factors (postnatal steroids, sepsis, NEC and mechanical ventilation > 3 days) were not different between cohorts.

The applied definition of BPD [16] may prove unsuitable for infants receiving automated oxygen titration. The general consensus is that during a day supplemental oxygen should be given for at least 12 hours to be counted towards the 28 days required for the diagnosis of BPD. During automated oxygen control the administered proportion oxygen may be only intermittently be above 0.21 in a 24-hour period, and this may not be predictive of BPD, for example when these brief moments are linked to apnoeic events. Depending on what criteria are used to define BPD, significantly more infants would be classified as having BPD.

Several measures were taken to minimise the risk of bias associated with retrospective chart studies, such as missing data from patients in regional hospitals. Given that the data are relatively recent and thanks to the modest cohort size, we were able to have two independent researchers check all electronic patient records and discharge papers from regional hospitals for the outcomes. Furthermore, respiratory support data was based on automatically stored data in our patient data management system, precluding human error. In 2017 our unit changed to single room care[28], and although there have been no other major changes in standard care besides type of ventilator, we cannot rule out that there are unmeasured changes that can influence results in either direction.

Importantly, the outcomes of some outcomes were rare (for example mortality and PVL) and it should be noted that the power of the study may not be sufficient to observe a difference in these outcomes between the groups. This is reflected in the broad relative risk confidence intervals, indicative that the true effect may be markedly different. Ultimately, the retrospective nature of this study precludes us from drawing definite conclusions on the causal effect of choice of algorithm on short-term clinical outcome. Further research is warranted to replicate these findings, preferably in a large multicentre randomised trial.

Conclusion

In this observational study, the OxyGenie epoch was associated with less morbidity when compared to the $CLiO_2$ epoch. There were significantly fewer infants that received treatment for ROP, received less intensive respiratory support and although there were more supplemental oxygen days, the duration of stay in the NICU was shorter. A larger study will have to replicate these findings.

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