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Outcomes after automated oxygen control for preterm infants

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Chapter 10

Summary

Introduction

This thesis consists of studies that relate to outcomes of preterm infants after using automated oxygen control (AOC). Supplemental oxygen is an important tool in battling hypoxia related to prematurity but can be harmful. Hyperoxia resulting from inappropriate oxygen administration can lead to morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity and neurodevelopmental impairment. Therefore, supplemental oxygen must be carefully titrated within a therapeutic range. An automated oxygen controller has been proven to be more successful than manual control in titrating oxygen within this range. In this thesis, a review is given of which algorithms are available, and how they work. Thereafter, we report on the effectivity of two automated oxygen controllers used in the NICU, followed by clinical and long-term outcomes after using AOC. We conclude with a general discussion of this thesis.

Currently available automated oxygen control algorithms

In **chapter 2**, we described the six automated oxygen control systems which are currently commercially available for use in the NICU. All systems are discussed in light of their algorithm, strategy and, if known, effect. Our goal was to provide guidance to clinicians seeking to comprehend AOC and those possibly seeking to implement this technology in their practice. We explained the basic approaches applied, namely rule-based, proportional-integral-derivative and the adaptive approach. Also, we gave an overview of how each of the six algorithms work and, where available, we gave an overview of clinical effect. When compared to manual titration, all these commercially available algorithms have shown a beneficial effect on the proportion of time that oxygen saturation of preterm infants is within the set target range, and they all demonstrate a decrease in hyperoxia and severe hypoxia. AOC may also reduce the workload for bedside staff. Although not reported to date, there is a concern that these devices may mask clinical deterioration. So far, trials involving different algorithms were heterogeneous in design and no head-to-head comparisons have been made, making it difficult to differentiate which algorithm is most effective and what clinicians can expect from algorithms under certain conditions.

Effectivity of automated oxygen control algorithms on oxygenation of preterm infants in the NICU

In **chapter 3**, we compared the effect of two different automated oxygen control devices on target range time and occurrence of hypoxic and hyperoxic episodes in a randomised cross-over trial in the Leiden University Medical Center. We included fifteen preterm infants born between 24 weeks and 29 weeks and 6 days of gestation, receiving invasive or non-invasive respiratory support. 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. The main outcome was time spent within the set oxygen saturation target range (TR; 91%-95% with supplemental oxygen, 91%-100% without supplemental oxygen). The infants in the study had a median gestational age of 26 weeks and 4 days (interquartile range (IQR) 25 weeks 3 days - 27 weeks 6 days) and a post-natal age of 19 (IQR 17-24) days. Time spent within the TR was higher during OxyGenie control (80.2 (IQR 72.6–82.4) % vs 68.5 (IQR 56.7–79.3) %, $p<0.005$). Less time was spent above TR while receiving supplemental oxygen (6.3 (IQR 5.1-9.9) % vs 15.9 (IQR 11.5-30.7) %, $p<0.005$) but more time was spent below TR during OxyGenie control (14.7 (IQR 11.8-17.2) % vs 9.3 (IQR 8.2-12.6)

%, p<0.05). There was no significant difference in time with SpO_2 <80% (0.5 (IQR 0.1-1.0) % vs 0.2 (IQR 0.1-0.4) %, p=0.061). Long-lasting SpO_2 deviations occurred less frequently during OxyGenie control. 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%), albeit at the cost of a small increase in mild hypoxaemia.

Chapter 4 is a continuation on comparing these two different automated oxygen control devices in preterm infants on time spent in different oxygen saturation ranges. Contrary to **chapter 3,** the entire stay in the NICU was investigated in a retrospective cohort study. Preterm infants (OxyGenie 75 infants, $CLiO_2$ 111 infants) born under 30 weeks of gestation receiving at least 72 hours of supplemental oxygen during respiratory support between October 2015 and November 2020 were studied. Inspired oxygen concentration was titrated by the OxyGenie controller between February 2019 and November 2020 and the $CLiO_2$ controller between October 2015 and December 2018 as standard of care. Time spent within the SpO_2 TR 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 (SpO_2 <80%: 0.7 [0.4–1.4] % vs 1.2 [0.7–2.3] %, p<0.001; SpO_2 >98%: 1.0 [0.5-2.4] % vs 4.0 [2.0-7.9] %, p<0.001). Both groups received a similar fraction of inspiratory oxygen (29.5 [28.0 – 33.2] % vs 29.6 [27.7-32.1] %, p=non-significant). Again, oxygen saturation targeting was better in the Oxygenie cohort, which resulted in less hypoxia and hyperoxia.

To conclude this part, we report what the effect is of using one-per-second or one-per-minute data in **chapter 5**. Large amounts of data are collected in neonatal intensive care units which could be used for research. It is unclear whether this data, usually sampled at a lower frequency, is sufficient for retrospective studies. We investigated what to expect when using one-per-minute data for descriptive statistics. One-per-second fraction of inspiratory oxygen and oxygen saturation data was processed to one-per-minute data and compared on average, standard deviation, target range time, hypoxia, days of supplemental oxygen, and missing signal. Outcomes calculated from data recordings (one-per-minute=92, one-per-second=92) showed very little to no difference. Neither did sub-analyses of recordings under 100 and 200 hours. In this study descriptive statistics of one-per-minute data were comparable to one-per-second and could be used for retrospective analyses. Comparable, routinely collected one-per-minute data could be used to develop algorithms or finding associations retrospectively.

Clinical and long-term outcome after using automated oxygen controllers for preterm infants during NICU stay

Several studies demonstrated an increase in time spent within target range when AOC is used, however the effect on clinical outcome remains unclear. In **chapter 6** we compared clinical outcomes of preterm infants born before and after implementation of AOC as standard of care. In a retrospective pre-post implementation cohort study of outcomes for infants of 24-29 weeks gestational age receiving respiratory support before (2012-2015) and after (2015-2018) implementation of AOC as standard of care were compared. Outcomes of interest were mortality and complications of prematurity, number of ventilation days and length of stay in the Neonatal Intensive Care Unit (NICU). A total of 588 infants were included (293 pre- vs 295 in the post-implementation cohort), with similar gestational age (27.8 weeks pre- vs 27.6 weeks post-implementation), birth weight (1033 grams vs 1035 grams) and other baseline characteristics. Mortality and rate of complications related to prematurity were not different between the groups. Length of stay in NICU was not different, but duration of invasive ventilation was shorter in infants who received AOC (6.4 ±10.1 days vs 4.7 ±8.3 days, p=0.029). In this pre-post comparison, the implementation of AOC did not lead to a change in mortality or morbidity during admission.

Faster resolution of hypoxaemic or hyperoxaemic events in preterm infants may reduce long-term neurodevelopmental impairment. Automatic titration of inspiratory oxygen increases time within the oxygen saturation target range and may provide a prompter response to hypoxic and hyperoxic events. In **chapter 7** we assessed routinely performed follow-up at two years of age after implementation of AOC as standard care and compared this with a historical cohort. Neurodevelopmental outcomes at two years of age were compared for infants born at 24-29 weeks gestational age before (2012-2015) and after (2015-2018) implementation of AOC as standard of care. Primary outcome was a composite of mortality or neurodevelopmental impairment (NDI), other outcomes assessed were mild-moderate NDI, Bayley-III composite scores, cerebral palsy and problem behaviour scores. 289 infants were eligible in the pre-AOC epoch and 292 in the post-AOC epoch. Baseline characteristics were not significantly different. 51 infants were lost to follow-up (pre-AOC 6.9% (20/289), post-implementation 10.6% (31/292)). The composite outcome of mortality or severe NDI was observed in 17.9% pre-AOC (41/229) vs. 24.0% (47/196) post-AOC (p=0.12). No significant differences were found for the secondary outcomes such as mild-moderate NDI, Bayley-III composite scores, cerebral palsy GMFCS and problem behaviour scores, with the exception of parent-reported readmissions until moment of follow-up which was less frequent post-AOC than pre-AOC. In this cohort study,

implementation of automated oxygen control in our NICU as standard of care for preterm infants led to no statistically significant difference in neurodevelopmental outcome at two years of age.

In **chapter 8** we compared short-term clinical outcomes after using two different automated oxygen controllers (OxyGenie and $CLiO_2$) in a propensity score matched retrospective observational study. Preterm infants (OxyGenie n=121, $CLiO_2$ n=121) born between 24+0-29+6 weeks of gestation were included. 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. Again, inspired oxygen was titrated by OxyGenie (SLE6000) or $CLiO_2$ (AVEA) during respiratory support. We compared mortality, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis and found that 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 had a shorter admittance 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 a significantly lower 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 between all other morbidities. 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.

Finally, this thesis concludes with discussing the results of our studies. Automated oxygen control is up and coming and improves oxygen targeting by reducing hypoxia, hyperoxia and workload. This thesis provides the first evidence that the success of oxygen targeting is influenced by choice of AOC device. The OxyGenie controller was more effective than the $CLiO_2$ controller, both in a controller crossover study as well as during the entire admission under routine clinical care. Ultimately our result demonstrated that OxyGenie is a better choice than $CLiO_2$ for oxygenation targeting. The effect on clinical outcome of these devices is not yet clear. OxyGenie control was associated with better clinical outcome than $CLiO_2$ control, but the retrospective nature of the studies performed precludes us from inferring causality. Nevertheless, all data in this thesis are pointing in the same direction.

In the future research on this topic will involve a direct head-to-head comparison of all ventilators, preferably under the same conditions. This could be achieved by testing all available algorithms against a model of a preterm infant. This will allow us to inform clinicians what to expect when using an algorithm/ventilator combination. Directly following my PhD, I started this project at the University of Tasmania in Australia under supervision of Prof Peter Dargaville with a team of clinicians and engineers. Furthermore, automated oxygen control gives us the tool to elucidate what the least harmful range to target is. Previous studies have struggled to provide this evidence as during significant overlap between the compared target ranges occurred, reducing discriminative power. Automated oxygen control will provide strict titration and prevent this overlap. We are currently testing an SpO_2 target range of 91%-95% against one of 92%-96%. Finally, further research should be done to provide strong evidence on the effect of automated oxygen control on clinical outcome, preferably using the most effective automated oxygen controller.