Title: Closed loop automated oxygen control in neonates – a review

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Short title: Neonatal closed loop automated oxygen control

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ABSTRACT

Aims: Neonates frequently require supplementary oxygen but may develop complications if the oxygen saturation is outside the target range. This review aimed to determine whether the algorithms used in closed loop automated oxygen control systems influenced their efficacy and whether use of the systems reduced relevant, long-term neonatal complications.

Methods: A literature search was conducted using PubMed and Google Scholar. The search terms were "closed loop" or "automat*", "oxygen" and "neonat*".

Results: Eighteen studies were identified: sixteen comparison clinical studies, an observational study and an animal study. Overall, closed loop automated oxygen control was associated with an increased percentage of time spent within the target oxygen saturation range and there were fewer manual adjustments to the inspired oxygen concentration when compared with manual oxygen control. The systems were effective in infants on non-invasive respiratory support or mechanically ventilated, but no study included term-born infants. No long-term data were available to determine if complications of oxygen toxicity were reduced.

Conclusion: Closed loop automated oxygen control has been shown in short term trials including preterm and low birth weight infants to improve target saturation achievement. Whether long term outcomes will be improved with their use requires investigation.

Key words: Closed loop automated oxygen control; neonate; bronchopulmonary dysplasia; retinopathy of prematurity

KEY NOTES

Closed loop automated oxygen control systems automate the adjustment of the inspired oxygen concentrations according to peripheral oxygen saturation levels. The systems result in the delivery of supplementary oxygen more often in the desired oxygen saturation target levels with less manual intervention. As yet, however, there is no evidence that their use reduces long term complications related to supplementary oxygen, this requires investigation.

INTRODUCTION

Neonates with respiratory distress frequently require supplementary oxygen (1), but its use can result in development of reactive oxide species (ROS) and complications such as bronchopulmonary dysplasia and retinopathy of prematurity (2). Targeting oxygen therapy to maintain oxygen saturations (SpO_2) within a predefined range (SpO_2 of 90-95%) can maximise the benefits of increased oxygen delivery to tissues whilst minimising the risk of complications (3, 4). As a consequence, in clinical practice, peripheral oxygen saturations are continuously monitored and used to guide adjustments to the inspired oxygen (FiO_2) which are made manually by neonatal practitioners. Neonatal patients are prone to frequent fluctuations in oxygen saturations, with as many as 600 intermittent hypoxic episodes documented in one week in one study (5). Compliance with SpO_2 target ranges has been shown to be variable even within the same patient over time, as well as between patients and centres (6). One quality improvement group found their target saturation range achievement was as low as 20% (7). Furthermore, narrowing the target range decreases compliance (6) and target achievement decreases as the number of patients per nurse increases (8). The shortfalls in target saturation range achievement have been suggested to be due to the clinical staff being more tolerant of SpO_2 levels which are too high rather than too low (9). In one study, upper alarm limits were set too high up to 76.5% of the time, whereas lower alarm limits were set correctly 91.1% of the time (9).

Closed loop automated oxygen control systems use SpO_2 values monitored in real time, to calculate and make an adjustment to the FiO_2 without any human

intervention. The resultant change in SpO_2 is monitored and further alterations to the FiO_2 made as needed. Closed loop automated oxygen control systems may, therefore, provide a solution for the low compliance to target oxygen saturation level, reduce the need for manual adjustments (and hence workload) and decrease complications.

Closed loop automated oxygen control systems continuously monitor SpO_2 and the data are fed into an algorithm which determines and executes an appropriate adjustment to the FiO_2. The result of this adjustment is monitored and further changes made if needed. The relationship between FiO_2 and SpO_2 in neonates needing respiratory support and supplemental oxygen is non-linear and complex (10), hence algorithms are used which reflect this. Several types of algorithm have been used.

A systematic review of clinical trials comparing closed loop automated oxygen control to manual control confirmed that these systems increase the time spent in target SpO_2 ranges in prematurely born infants (11). We have undertaken a literature review of closed loop automated oxygen control in neonates, aiming to determine their efficacy in those born prematurely or at term. Our aims were also to describe the algorithms employed and if their performance differed and whether use of closed loop automated oxygen control resulted in reductions in adverse outcomes, as well as increasing the time spent in the target oxygen saturation range.

METHODS

Literature searches were completed on Google Scholar and Pubmed using the terms "closed loop" or "automat*" and "oxygen", "neonat*". Included studies were those comparing the use of closed-loop automated oxygen control systems with manual or steady-state oxygen control. The inclusion criteria were published studies that compared the use of closed-loop oxygen monitoring devices to manual or steady-state (unchanged) oxygen control with measured outcomes of time spent within target oxygen saturation range and/or number of manual adjustments to the fraction of inspired oxygen. Exclusion criteria were studies that either did not involve neonatal patients or animal studies which did not model neonatal patients' respiratory diseases. One thousand, one hundred and forty results were identified. Abstracts were screened for relevance and duplicates removed. One hundred and forty-three studies remained, but only nineteen were studies of closed loop automated oxygen control relating to neonatal practice (Table 1).

RESULTS

Eighteen studies were identified as relevant to neonatal practice: sixteen comparison, clinical studies, an observational study and an animal study. All the clinical studies were in infants of gestational ages between 23 and 30 weeks, that is there were no studies involving infants born at term. A variety of algorithms were used.

1. Algorithms used in closed loop automated oxygen monitoring

Rule-based algorithms

Rule-based, fuzzy algorithms operate by measuring the error and making an adjustment based on the magnitude of the error (12, 13). Fuzzy logic is used to represent the idea that a statement could vary from completely true to completely false, including being partially true or partially false, whereas non-fuzzy logic only enables a statement to be defined as 'true' or 'false'. This approach is helpful for systems which have non-linear relationships, such as the relationship between SpO_2 and FiO_2 in a neonate (14). This allows the knowledge and expertise that medical staff have to translate more easily into an algorithm (13), as staff would describe a patient's SpO_2 level as being slightly low or extremely low rather than 'just' low.

Rule-based algorithms determine adjustments based on the current SpO_2 and the trend of SpO_2 levels. The trend is calculated from the size of the error (how far away the SpO_2 is from the mid-point of the target range), its velocity and its acceleration. The trend determines what adjustment, if any, is made to the FiO_2 (14). For example, a closed-loop automatic control (CLAC) algorithm used in a randomised controlled trial (15) determined whether the SpO_2 was in the normal range, above or below (including the magnitude of the error) and whether it was increasing, decreasing or stable and then suggested five possible FiO_2 adjustments from -0.02 to +0.05. Additionally, the algorithm recognised when the SpO_2 signal was poor and excluded those readings (15). Similar rule-based algorithms have been used in preterm lambs, with significantly more time spent in target SpO_2 range under closed loop automated

control compared with manual control during a period of stable ventilation (post-resuscitation) (16).

Proportional-integral-differential (PID) algorithms

PID algorithms use the error, its integral and its derivative to determine the output, with multiplying coefficients (or gains) applied to each of the inputs). The error, as in rule-based algorithms, is the difference between the current SpO_2 and the midpoint of the target SpO_2 range. Some PID algorithms automatically adjust the gains over time in order to re-model the algorithm appropriately for that patient's respiratory system (17).

Adaptive model algorithms

Adaptive model control algorithms aim to model the patient's relationship between FiO_2 and SpO_2 based on the oxygen dissociation curve. The adaptive control model algorithm uses this curve to determine how much the FiO_2 needs to be adjusted to cause the desired change in SpO_2 and adjusts the model at set intervals (every two to five minutes) to make it more accurate for that particular patient (18).

Comparison of algorithms

All three algorithms have been shown to increase the amount of time spent in the target saturation range (10) and decrease the number of manual interventions required (10). The adaptive model control algorithm has been shown to result in the largest increase in time spent within the target saturation range compared to manual control (60% compared to manual control, whereas the PID algorithm achieved 52% and the rule-based algorithm achieved 56% when compared to manual control) (10).

Additionally, the adaptive model algorithms require no setup, as the algorithm automatically adjusts to the patient's response (10).

2 Accuracy of closed loop automated oxygen therapy

Sixteen single or multicentre clinical studies have been undertaken comparing closed loop automated oxygen control to manual oxygen control in neonates to determine whether automating FiO_2 control was associated with a greater target SpO_2 achievement. They consistently demonstrated that closed loop automated oxygen control maintained the patient within their target SpO_2 range a significantly greater proportion of the time than manual control (10, 12, 15, 16, 19-30). Closed loop automated oxygen control has been demonstrated to reduce hyperoxic episodes, in one study almost halving the frequency (9.3 to 4.7 episodes per 90 minutes) and the duration (19.3s to 10.1s) of hyperoxic episodes (21) and in another study reducing the median percentage time spent with an SpO_2 >95% from 41.9% to 19.3% ($p<0.001$) (28). A randomised crossover study found that an automated controller resulted in 'overshoot' (an exaggerated response to hypoxia leading to hyperoxia) more frequently than manual control, but the resulting episodes of hyperoxia were shorter than similar episodes under manual control (30).

A systematic review (11) of closed loop automated oxygen control studies found that automated control of FiO_2 resulted in a significantly higher time spent in the target saturation range (mean difference (MD) 12.8%, 95% CI 6.5-19.2%). It also found that automated control resulted in significantly reduced periods of hyperoxia (MD: -8.8%; 95% CI: -15 to -2.7%), severe hypoxia (MD: -0.9%; 95% CI: -1.5 to -0.4%) and the number of hypoxic events (MD: -5.6; 95% CI: -9.1 to -2.1%) (11). One

study, however, found that automated control was associated with an increase in the number of episodes of hypoxia, although there was no increase in the episodes of extreme hypoxia (SpO_2<80% or <75%) (23).

Applying automated O_2 under different conditions

Automated systems have been shown to increase the percentage of time spent in the target oxygen saturation range for patients at a range of postnatal ages, despite oxygen stability varying with postnatal age. As before, none of these studies have included term born infants. They have also been shown to be effective for infants who were intubated and ventilated (10, 20, 22-24), as well as those on non-invasive respiratory support (12, 19, 21, 25, 27, 30). In a randomised trial of a closed loop automated oxygen control system for infants on non-invasive respiratory support, infants on automated control spent a significantly higher proportion of their time within their target saturation range compared to those on manual control (58% versus 33.7% respectively) (12). The automated system was also associated with a reduction in the frequency and duration of episodes of hyperoxia (12).

Comparison with optimum manual control

Automated oxygen control has been compared with routine manual control as described above, but also with optimum manual control that is one to one dedicated attention to FiO_2 adjustment. Automated control was superior to one-to-one attention to oxygen adjustment in maintaining SpO_2 within the target range (81% of the time versus 69%) (17). A study of automated control in preterm infants on non-invasive respiratory support found that it provided a significantly increased percentage of time within the target range when compared to ‘best’ manual control (78% versus

55% in the target SpO_2 range, p=0.0001) (27). In that study, prolonged periods outside of the target saturation range were almost eliminated by automated control with no 60-second episodes with SpO_2 levels >96% or <85% and fewer than two episodes lasting 30 seconds (27). This suggests that even with the best possible staffing ratios, automated oxygen control will still confer a benefit to patients.

Comparison with different oxygen saturation ranges

A crossover trial of infants with closed loop automated SpO_2 control compared two target saturation ranges: 87-93% and 90-93% (31). The tighter target range narrowed the distribution of SpO_2 values, but did not result in any significant reduction in the frequency or duration of episodes of desaturation, increase the time spent within the target SpO_2 range, or decrease the time spent at extremes of SpO_2 (31). A further study compared two other target SpO_2 ranges: 89-93% and 91-95% (25). The automated oxygen control system significantly increased the time spent within the target saturation range with both target SpO_2 ranges compared to manual control (25). The effect was larger in those with the lower target SpO_2 range group (a difference of 8% compared to 4% more time in the target saturation range), although this appeared to be due to less effective manual control in that group (25).

Supplementary oxygen weaning

A crossover study found that with automated weaning, infants spent significantly more time with a FiO_2 <0.25 than with manual control (23). A further crossover study of automated FiO_2 control versus manual control in infants on nasal cannula oxygen found that, in addition to automated control resulting in a significantly greater proportion of time with saturations within the target range, the automated

control also tended to result in a FiO_2 of 21%, whereas manual control resulted in an FiO_2 of 30% (30). Those results suggest automated control might identify which patients no longer require supplementary oxygen more quickly. The results of a systematic review of automated control, however, did not demonstrate a significant difference in FiO_2 exposure or time spent below the target SpO_2 range (11). More evidence is required to determine whether automated control will aid weaning and in which groups of patients.

Other outcomes

No data were reported on adverse effects of closed-loop oxygen control, although the majority of the included studies provided the option for manual overriding of the automated systems in the case of an unsafe alteration to the FiO_2. No data were found on the long-term clinical outcomes for infants with closed-loop oxygen control as compared to those with conventional manual control. A large, multicentre randomised controlled trial including long-term outcomes is underway and expects to complete in 2022 (32).

3. **Decrease in staff workload**

Multiple studies have found that automated oxygen control systems lead to a decrease in the number of manual interventions made by staff (10, 12, 15, 20, 21, 23-25, 27, 29). Studies have reported that clinical staff needed to adjust the FiO_2 less than once per hour when there was automated control (10, 12, 21, 24, 27, 29), compared to as many as 29 times per hour during manual control (20). A randomised study of one automated FiO_2 system found that the automated system

made 7,540 FiO_2 adjustments in a 12-hour period, whereas staff made 80 adjustments over the same time period in the manual control group (12). Furthermore, the staff did not make any manual adjustments to the automated control group's FiO_2 (12), suggesting that they thought the automated adjustments were all deemed appropriate.

In a crossover study, staff adjusted the FiO_2 2.3 times/hour during manual control, whereas the automated system adjusted the FiO_2 64 times/hour (27). The frequency of adjustments may contribute to the overall increase in target saturation achievement with automated oxygen control (11). No evidence, however, was available to suggest that the reduction in manual interventions resulted in neonatal practitioners having a reduced workload and hence able to use that time for other care activities.

4. Critical analysis of included studies

Similarly, to Mitra's systematic review, we found a high risk of bias. This was mostly due to the fact that, although the majority of studies were randomised crossover studies, few details of the randomisation process and sequence generation were described. One study was observational, therefore, introducing a risk of confounding factors (such as gestational age or disease state) although the authors did report that the demographics of the two sets of patients were not statistically significant (28).

DISCUSSION

This review highlights that automated oxygen control does increase the percentage of oxygen saturation levels within the target range. It should be noted, however, that even with automated systems the time infants spend in the target span of SpO_2 is still far from satisfactory and that there is much room for improvement. It also reduces the number of manual modifications made to the FiO_2, but whether this reduces the nursing workload enabling improvements in clinical outcome by nurses being able to concentrate on other tasks has not been documented. Furthermore, whether automated oxygen control reduces long term complications has not been investigated.

There are, however, some concerns regarding automated oxygen control. Body movement is known to be a common cause of disruption of SpO_2 signal, but it can also be associated with hypoxaemia. Some automated systems are designed not to adjust FiO_2 if the SpO_2 signal is of a poor quality. Therefore, there could be a delay in reaction to hypoxaemia until the signal quality is restored (33). Episodes of desaturation are commonly used as a potential warning sign of infection or respiratory deterioration (34). An automated FiO_2 system could potentially 'mask' this important clinical sign by maintaining the SpO_2 within the target range. Therefore, some systems have additional alarm features to signal a significant increase in FiO_2 even if the SpO_2 remains within the target range. For example, one system activates an alarm if there is an increase in FiO_2 of ≥ 0.3 from the basal level (23).

In conclusion, automated oxygen control does reduce the time spent in which the oxygen saturation level is outside the target range. It is, however, important to determine whether this improves long term complications related to oxygen toxicity and if use of such systems reduces nurse workload which translates into improved clinical outcomes.

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LIST OF ABBREVIATIONS

CLAC	Closed loop automatic control
CPAP	Continuous positive airway pressure
FiO_2	Fractional concentration of inspired oxygen
MD	Mean difference
NCPAP	Nasal continuous positive airway pressure
PaO_2	Partial pressure of oxygen in arterial blood
PID	Proportional integral differential
RDS	Respiratory distress syndrome
ROS	Reactive oxide species
SpO_2	Oxygen saturation measured by pulse oximetry

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Table 1: Included studies

Author (Year)	Type of study	Population	N	Algorithm	% time spent in target SpO_2 range		Number of manual adjustments		Results
					Manual	Automated	Manual	Automated	
Morozoff (2017) (10)	Crossover study	Low birthweight, ventilated, preterm	7	State machine	35**	56**	3.5/study period *	0/study period *	• Increased time within target range with all three algorithms tested compared to manual control • All algorithms significantly reduced time spent in hyperoxaemia • Algorithms did not reduce hypoxia
				Proportional-integral-derivative	41*	52*	2/ study period *	0/study period *	
				Adaptive	40**	60**	2.5/ study period **	0/study period **	
Zapata (2014) (12)	Randomised controlled trial	<30 weeks gestation, <1000g birthweight, nasal cannulae, episodes of hyperoxia & hypoxia	20	Rule-based, fuzzy	33.7**	58.0**	80/120h	0/120h	• Increased time within target range with automated control • Reduced frequency and duration of hyperoxic episodes • Fewer episodes of SpO_2 70-75% with automated control, but increased percentage of time with SpO_2 <85%
Hallenberger (2014) (15)	Multicentre randomised controlled crossover study	<37 weeks gestation using mechanical ventilation or NCPAP; FiO_2 ≥0.25	34	Rule-based, non-fuzzy	61.0***	72.1***	77/24h*	52/24h*	• Significant increase in mean time spent in target SpO_2 range shown in 3 out of 4 participating centres • Lowest effect seen in centre with lowest SpO_2 target range • Significant reduction in time spent below the target range

Hutten (2015) (16)	Randomised study	Preterm lambs from newborn resuscitation	19	Rule-based	84.0*	93.2*	13.0/h	5.7/h	• Increased time within target range with automated control during steady-state ventilation • Automated FiO_2 feasible to be used during resuscitation and surfactant administration
Bhutani (1992) (17)	Randomised crossover study	Preterm infants previously ventilated for RDS, studied receiving supplemental O_2	14	Adaptive	69	81	-	-	• Adaptive control increased time spent within the target range compared to manual control • Minimal overshoot seen with adaptive control
Morozoff (2009) (18)	Crossover study	Low birthweight, ventilated preterm infants	7	State machine	57	71	3.74/h	0.48/h	• All three algorithms tested increased time spent within target range when compared to manual control • As the target range increased, the three algorithms converged towards equivalent performance • Adaptive model did not require manual tuning to adjust to changes in patient physiology
				Proportional-integral-derivative	57	70	3.74/h	0.45/h	
				Adaptive	57	73	3.74/h	0.23/h	
Beddis (1979) (19)	Crossover study;	Preterm, respiratory distress syndrome receiving supplemental oxygen	12	Rule-based	72.4**	87.8**	-	-	• Increased time within target range with automated control • Reduced time with PaO_2 below target range with automated control • No significant difference in time with PaO_2 above target range • Shorter duration of episodes outside of target range with automated control

Claure (2001) (20)	Randomised crossover study	Preterm infants, <1500g birthweight, mechanically ventilated with frequent episodes of hypoxaemia	14	Rule-based combined with differential feedback	66.3*	74.9*	29/h	n/a	• Increased percentage of time spent in normoxaemia with automated control • No significant difference in frequency or duration of hypoxaemic or hyperoxaemic episodes • No significant difference in mean FiO_2 supplied
Urschitz (2004) (21)	Randomised controlled crossover study	<34 weeks gestation, NCPAP and supplemental oxygen	12	Rule-based, non-fuzzy	81.7*	90.5*	3.0/h***	0.3/h***	• 11% increase in time spent within target range with automated control • Reduced frequency and duration of hyperoxic episodes • Reduction in SpO_2 fluctuations
Claure (2009) (22)	Randomised crossover study	Preterm, mechanically ventilated with frequent episodes of hypoxaemia	16	Proportional-integral-derivative	42***	58***	7/4h***	34/4h***	• Increased time within target range with automated control • Reduced time in hyperoxaemia and time spent with SpO_2 above the target range with automated control • Increased frequency of episodes with SpO_2 <88% with automated control • Slight decrease in duration of hypoxaemic episodes with automated control
Claure (2011) (23)	Multicentre randomised crossover study	Preterm infants, mechanically ventilated, SpO_2 instability	34	Proportional-integral-derivative	32***	40***	112/24h***	10/24h***	• Increased time within target range with automated control • Reduced duration of hyperoxia • Consistently lower FiO_2 throughout the study period with automated FiO_2 • Increased frequency of hypoxia

Lal (2015) (24)	Randomised crossover study	Preterm, mechanically ventilated	27	Proportional-integral-derivative	59.6*		72.8*	63/12h**	0/12h**	• Increased time within target range with automated control • Reduced time with SpO_2 >98% or <80% • Reduced prolonged episodes of hypoxaemia and hyperoxaemia (≥1 or ≥3 minutes)
Van Kaam (2015) (25)	Multicentre randomised crossover study	<33 weeks gestation, mechanically ventilated or receiving non-invasive respiratory support	80	Proportional-integral-derivative	SpO_2 target 89-93%	54**	62**	-	-	• Mean within subject difference was significantly larger in the 89-93% target group • Reduced time in hypoxaemia and hyperoxaemia • In the 89-93% target group only: reduced time above target range, reduced severe hyperoxaemia and reduced episodes of prolonged hyperoxaemia
					SpO_2 target 91-95%	58*	62*			
Waitz (2015) (26)	Randomised crossover study	<30 weeks gestation, mechanically ventilated or CPAP/NCPAP, intermittent hypoxaemia	15	Proportional-integral-derivative	69.1**		76.3**	-	-	• Increased time within target range with automated control • Reduced time in hyperoxaemia • Reduced prolonged periods with SpO_2 <88% • No significant difference in cerebral tissue oxygen saturation between the two methods
Plottier (2017) (27)	Crossover study	<37 weeks gestation, non-invasive respiratory support	20	Proportional-integral-derivative	55****		78****	2.3/h	0.24/h	• Increased time within target range with automated control • Reduced SpO_2 coefficient of variation • Reduced time spent with SpO_2 < 80% or >98% • No overshoot with automated control
Van Zanten (2017) (28)	Prospective observational study	<30 weeks gestation, mechanically ventilated or non-invasively	42	Proportional-integral-derivative	48.4**		62.0**	-	-	• Increased time within target range with automated control • Reduced time with SpO_2 above target range • Increased time with SpO_2 between 80-

		ventilated							90% but no increase in time with SpO_2 <80%
Gajdos (2018) (29)	Randomised crossover study	<30 weeks gestation, non-invasive or invasive ventilation, SpO_2 instability	12	Proportional-integral-derivative	68.52**	77.83**	7.5/h***	0.5/h***	• Reduced time in hypoxaemia, including a reduction in prolonged periods of hypoxaemia >60s and >180s duration • No significant difference in time spent above the target SpO_2 range • No significant difference in hepatic or cerebral tissue oxygen saturation between the two methods
Reynolds (2018) (30)	Two-centre randomised crossover study	Preterm, receiving high-flow oxygen	30	Used discrete target value, SpO_2-FiO_2 relationship and dynamics of response	49****	80****	1.6/h****	0/h****	• Increased time within target range with automated control • Reduced variation of SpO_2 values • Reduced time below target range and with SpO_2 <80% • Reduced time with SpO_2 above target range • No significant difference in frequency of episodes of hyperoxaemia

* = $p < 0.05$
** = $p < 0.01$
*** - $p<0.001$
****- $p<0.0001$