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Narrative review of closed loop automated oxygen systems

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ABSTRACT

Preterm infants frequently require respiratory support with supplemental oxygen but excess and fluctuation of oxygen levels can have adverse effects. Oxygen saturation levels are maintained within narrow target ranges as a manual titration process. Closed loop automated oxygen systems hypothesis that automatic titration of inspired oxygen will reduce time spent out of desired oxygen target range compared with current manual control.

Aims: comparison of automated versus manual oxygen control for preterm neonates undergoing non-invasive ventilation plus supplemental oxygen.

Methods: Four electronic databases (CINAHL, Cochrane Library, Medline and PubMed) were searched with narrative review of findings.

Results: Four studies were included and all reported neonates spent more time in the oxygen target range with automated versus manual control with a wide variation in improvement from 8.8% to 30%.

Conclusions: Automated oxygen systems with non-invasive respiratory modalities can minimise time spent out with oxygen target range. Long term impact of automated control on incidence of oxidative stress injury remains undetermined.

1. Introduction

A leading cause of respiratory compromise in the newborn is premature birth. For many, their immaturity results in the need for assisted respiratory support and additional supplemental oxygen therapy. Whilst oxygen is required for homeostasis, it can be the cause of iatrogenic harm in the neonate (Poets et al., 2015). The mechanism of harm is multifactorial but fluctuations in the fraction of inspired oxygen (FiO_2) and episodes of hypoxia and hyperoxia are thought to be major contributors of neonatal mortality and morbidity. Consequently, the oxygen saturation level (SpO_2) and the FiO_2 being delivered to the neonate must be continuously monitored to maintain both within a desired target range. Manual adjustments to the FiO_2 to maintain the SpO_2 within the target range can be challenging for the neonatal nurse at the cot side (Harris et al., 2020). In recent years, closed loop automated oxygen systems (CLAOS) have been introduced into neonatal practice. These have software algorithms which automatically adjust the FiO_2 in response to fluctuations of the infants' SpO_2 to maintain a predetermined oxygen target range.

1.1. Background

There are a variety of conditions which result in neonates receiving respiratory support with supplementary oxygen, potentially for prolonged periods of time. Prompt titration of FiO_2 is essential as both periods of hypoxia and hyperoxia are known to result in adverse outcomes for premature infants. Oxygen consumption leads to the production of reactive oxygen species, which are a by-product of aerobic respiration and cellular metabolism. Reactive species are inactivated by a variety of antioxidant mechanisms in a continuous process, however, during periods of excess oxygen overproduction of reactive species occurs leading to oxidative stress (Perrone et al., 2017). Accumulation of reactive species in the cell can result in membrane damage, lipid peroxide formation and eventual apoptosis (Wedgwood and Steinhorn, 2014). Hyperoxia associated with oxidative damage can lead to long term complications such as bronchopulmonary dysplasia and retinopathy of prematurity but additionally periods of hypoxia are recognised as causing detrimental effects on the brain, pulmonary vasculature, gastrointestinal tract, and other tissues (Claure and Bancalari, 2013).

The optimal range of SpO_2 for premature infants is unknown but it is common practice to have a target range of 90–95% (Ali et al., 2020).

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Manual adjustment to the FiO_2 to maintain SpO_2 within the target range can be challenging for the neonatal nurse at the cot side and is time consuming and often unsuccessful (Van Zanten et al., 2017). Studies have shown that compliance with the target range is difficult to achieve (Harris et al., 2020), resulting in neonates spending only an estimated 50% of the time in the desired target range (van Kaam et al., 2015). Nursing response to SpO_2 alarms are likely to reflect a pragmatic approach, firstly excluding confirmed loss of oxygenation, artifact or disconnection of monitor (Sturrock et al., 2020). A low alarm requires an increase in FiO_2 to minimise hypoxaemia but can create an overshoot of the upper limit as oxygenation improves and the neonate recovers, requiring frequent and timely adjustments to avoid hyperoxia. Nurses use their clinical judgement and knowledge of the individual neonate to maintain SpO_2 target range parameters thus compliance is variable and deteriorates as the ratio of nurse-to-patient increases; or varies nurse to nurse, patient to patient. This variability increases the risk of complications, costs of care and length of stay in hospital (Hagadorn et al., 2006).

Over the last 20 years software algorithms for closed loop automated oxygen control systems have been designed and implemented into respiratory support devices. The aim is to automatically adjust the FiO_2 depending on the infants' SpO_2 thus improving the percentage of time spent within the set target range. A CLAOS has 3 features: a sensor, a controller, and an actuator. To obtain an oxygen saturation, the sensor monitors the oxygen level and produces a signal; the controller determines the difference between the signal and the set point on the monitor and the actuator translates the signal to a physical response which either increases or decreases the FiO_2 in order to maintain the infant within the target range (Brogi et al., 2017). To date the use of these algorithms have focussed on neonates receiving invasive and or mixed ventilatory support modalities but invasive ventilation is no longer the primary form of respiratory support in this population. Advances in neonatal care have resulted in non-invasive ventilatory support modalities being the preferred strategy of respiratory support for preterm infants when clinically possible (Breathnach & Sheahan,2017; Bresesti et al., 2019).

This is a narrative review of the current research evidence comparing CLAOS vs manual O_2 titration on maintenance of target range in preterm infants managed on non-invasive ventilation plus supplemental oxygen.

1.2. Aim

The aim of this review is to compare closed loop automated oxygen delivery systems (CLAOS) versus manual oxygen titration on the maintenance of oxygen saturation (SpO_2) within a designated target range for premature neonates requiring non-invasive respiratory support with supplemental oxygen.

Outcomes of interest include time neonates spent in designated oxygen target range, episodes outside of designated oxygen target range, FiO_2 limits, and comparison of algorithms used. Furthermore, the review aims to explore the current evidence base to guide future research and healthcare professional practices to optimise treatment for these neonates.

2. Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010) was adopted for this review. Scoping was undertaken to identify terms for the development of the PICO (Populations, Intervention, Comparators, Outcomes) element of the search strategy (Eriksen and Frandsen, 2018).

2.1. Search strategy

A computerized literature search was conducted for studies published in the following databases: CINAHL, Medline, PubMed and Cochrane Library. To describe the research, the following topics were defined: infant premature, infant low birth weight, premature*, neonat*, closed-loop, automat*, non-invasive, invasive, manual, oxygen range, O_2, hypoxia, hyperoxia. Prematurity was determined as infants born less than 34 weeks post menstrual age (PMA). The PICO synonyms and Boolean's operators AND were used for each database to combine the keywords, identifying articles containing two or three keywords and OR was used to expand the search and increase the number of studies which contain both subjects.

Eligible papers required the full text to be available in English, study design of randomised controlled trials and cross over trials, and published between January 2000 and January 2021 as the use of closed system oxygen is a relatively new technology. The reference lists of all relevant papers were scrutinised along with citation searching of the included studies and literature reviews to identify any other eligible studies. The first author initially made the assessment of eligibility for inclusion and then discussed this with supervisor to reach a final decision.

2.2. Data extraction and synthesis

A data-extraction form was used to summarize data for evidence synthesis. Each paper was read systematically several times. Data on both primary and secondary outcomes was included. Details on the sponsorship of the research was included as part of the consideration of external influences on the outcomes reported.

3. Results

The initial search identified 61 articles. The 61 records were reduced initially to 50 on title review, then a further 36 excluded with manual application of PICO major subject headings. The 14 full-text articles were read in their entirety and 10 were excluded due to ineligible research methodology used or a combination of respiratory therapies. These studies reported either RCT's or cross-over trials with a combined participant number of 342; two retrospective studies with a combined sample size of 106 and one prospective cross-over study with 20 participants. Of the 14 articles, 9 included both invasive and non-invasive modalities and the data were not distinguishable between these. A total of 4 quantitative studies were identified as being specific to non-invasive ventilation modalities and fulfilled the inclusion and exclusion criteria of the search strategy (Reynolds et al., 2019; Plottier et al., 2016; Zapata et al., 2014; Urschitz et al., 2004).

A data flowchart details the screening process and the number of records obtained after each screening (Fig. 1). A total of 4 papers that met the inclusion criteria were identified.

3.1. Critical appraisal

The four studies were assessed using the appropriate Critical appraisal skills programme checklists and a risk of bias comparison conducted (Table 1). An investigation of the differences and similarities in the studies and the risks of bias in each study forms part of the data synthesis. Due to the insufficient incompatible data meta-analysis was not considered possible and a narrative synthesis was undertaken. Relevant data on primary and secondary outcomes formed a data extraction table (Table 2).

3.2. Participants

The four studies resulted in a total of 82 preterm infants who received non-invasive respiratory support and supplemental oxygen titrated with CLAOS.

Sample size ranged from 12 to 30 infants.

All four studies had similar eligibility criteria with inclusion of preterm infants less than 37 weeks PMA receiving supplemental oxygen and

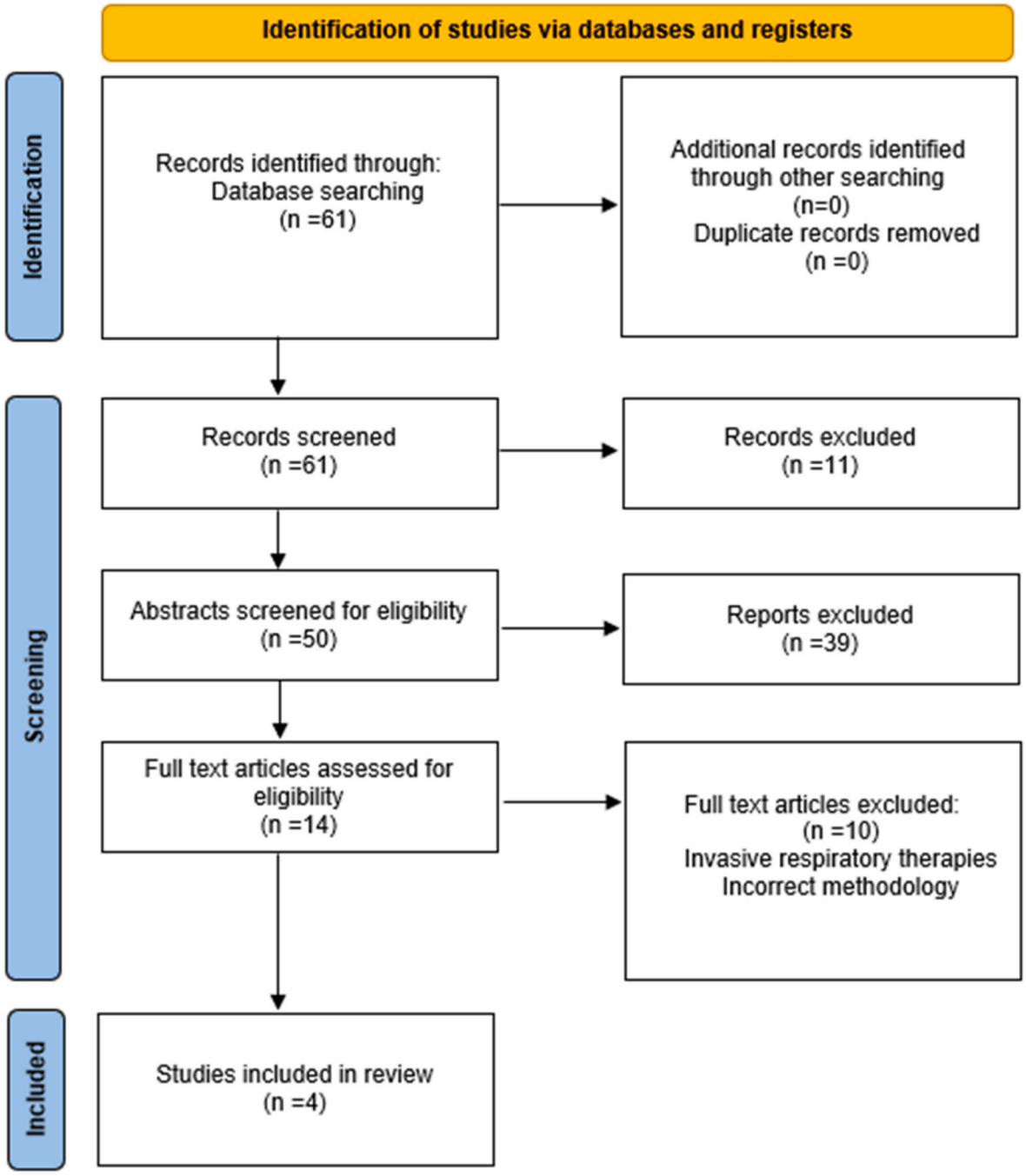

Fig. 1. Dataflow chart (Page et al., 2021).

exclusion criteria of infants with congenital anomalies or haemodynamic instability.

3.3. Study methods

Zapata et al. (2014) included 2 independent groups with participants randomly assigned to one of the groups using sealed envelopes. The study period was 12 h giving potentially 7200 min of data per group for analysis. No information was given about potential confounders between groups.

Reynolds et al. (2019) used a repeated measures (cross over) design with a study period for each arm of 24 h consecutive run.

Urschitz et al. (2004) also used a repeated measures (cross over) design but randomised participants to one of three different study groups of 5 modalities, each of which represented a fixed order of intervention and monitoring lasting 90 min each.

Plottier et al. (2016), used a repeated measures (cross over) design with the CLAOS arm flanked by two control arms of manual titration and therefore no randomisation took place. Participants were monitored for 12 h with each period being 4 h duration with a 15-min washout period between manual and automated titration.

All studies data collection method was continuous monitoring of physiological parameters as measured by SpO_2 monitor. The brand of monitor and algorithm varied between studies.

3.4. Primary outcome: time within the designated target range

The studies demonstrated that CLAOS, when compared to manual

Table 1
Risk of bias.

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)	Other biases
Reynolds, 2019	?	−	+	+	?	?	+
Plottier, 2016	?	−	+	−	?	+	−
Zapata, 2014	+	−	+	+	+	−	−
Urschitz, 2004	?	−	+	+	+	?	−
Quality assessment scale	+	High	−	Low	?	Unclear	

titration of FiO_2, resulted in preterm neonates spending more time within the desired oxygen target range. While this was statistically significant of all the included studies, there was considerable variation between the percentage extremes of time spent within target range. Urschitz et al. (2004) reported the closest variation with 90.5% vs 81.7% while the most extreme was reported by Plottier et al. (2016) with 78% vs 45%.

3.5. Secondary outcome: hypoxia episodes

Hypoxic episodes, when the neonate's oxygen saturation level was below the desired target range, were considerably reduced with the use of CLOAS.

Reynolds et al. (2019) reported the greatest reduction reporting CLAOS 12% versus 28% manual episode with duration between 17 s and 42 s respectively. This study findings also showed the proportion of time with a SpO_2 of <80% and <70% were less with automated compared to manual control. Urschitz et al. (2004) reported the number and mean duration of hypoxic episodes with CLAOS was 9.3 s versus 12.7 s manual control and noted the duration was shorter. Plottier et al. (2016) also demonstrated improvements in maintaining SpO_2 within the target range. Zapata et al. (2014) gave no specific data but noted that there was an increased frequency of episodes of SpO_2 within the range of 80–85% in automated as compared to manual modes but that the duration was shorter, 7 vs 15 s. However, there was an increased number of episodes of SpO_2 less than 70% in manual mode.

3.6. Secondary outcome: hyperoxia episodes

Hyperoxia was reported differently according to each study. Reynolds et al. (2019) categorised hyperoxia as SpO_2 as >95%, and found a lower proportion of time in hyperoxia in automated arm 12% vs manual arm 23%. However, neonates experienced more hyperoxia episodes in the automated arm than the manual arm but these were of a shorter duration. This finding was also reported in the study by Plottier et al. (2016) with a much greater variation in the duration of hyperoxia from 5.1% automated to 25% during manual control.

3.7. Secondary outcome: FiO_2 levels and adjustments

Reynolds et al. (2019) found that the mean FiO_2 was greater in the automated arm than manual arm but Plottier's study (2017) found that the oxygen requirements did not differ between automated and manual control.

Reynolds et al. (2019), Plottier et al. (2016) and Zapata et al. (2014), found considerably more adjustments were made to FiO_2 during the automated than manual periods. Reynolds et al. (2019) found 96 vs 1.6 FiO_2 adjustments/hour while Plottier et al. (2016) reported 64 vs 2.3 adjustments/hour automation vs manual mode. Zapata et al. (2014) reported adjustments as an overall figure and found the same pattern as other with 7540 adjustments during the 12-h automated period compared with 80 adjustments during manual control.

3.8. Secondary outcome: differences in algorithms

The differences in achieving the desired target oxygen range and minimising time outside of the range may have been affected by the choice and settings within the algorithms. Several algorithms were used with these differing in averaging times; responsiveness to magnitude and speed of SpO_2 change/FiO_2 change; motion detection and elimination effect criteria and patient specific parameters. The Clio2 (Urschitz et al., 2004) system performed best with achievement of target range 90.5% of time whereas the Auto-Mixer (Zapata et al., 2014) was least successful with achievement of target range 58% of the time.

Table 2
Data extraction.

Author & Year	Oxygen control algorithm	Type of study	Sample	Respiratory mode	In target oxygen range	Data Analysis	Results	Sponsorship
Reynolds et al. (2019) United Kingdom	IntellO_2	Randomised cross-over study	N = 30 GA 26 (24–27) weeks PNA 29 (18–53) days weight 1080 (959–1443) g.	HFNC	Time in TR; SpO_2 90–95%	Descriptive statistics for demographics. Wilcoxon signed-rank test for intervention outcomes.	Time in TR CLAOS 80% (IQR 70%–87%) vs manual 49% (IQR 40%–57%); $p < 0.0001$. Episodes SpO_2 <80% at least 60 s CLAOS 0 (IQR 0–1.25) vs manual 5 (IQR 2.75–14). Number of episodes SPo_2 >98% (4.5 (IQR 1.8–8.5) vs 5.5 (IQR 1.9–14); $p = 0.572$)	Study sponsored by vapotherm; some competing interests declared.
Plottier et al. (2016) Australia	VDL 1.0	Cross-over study	N = 20 GA 27.5 (26–30) weeks PNA 8 (1.8–34) days	HFNC (7) NCPAP (13)	Time in TR; SpO_2 91–95% (A) 90–94% (M)	Descriptive statistics for demographics. Wilcoxon signed-rank test for intervention outcomes	Time in TR: CLAOS 81 (76–90) %, vs manual 56 (48–63) %. $p < 0.001$. Changes to FiO_2 CLAOS 0.24/hour vs manual 2.3/hour	Research grant funded
Zapata et al. (2014) USA	Auto-mixer	Randomised Control Trial	N = 20 GA 27.3 weeks ± 1.7 SD (M&A); PNA 9 (M) 8 (A) 5–14 days	HFNC (6 M) HFNC (5 A) Supplemental oxygen (9)	Time in TR; SpO_2 85–93%	Descriptive statistics for demographics. Levene test and ANOVA for intervention outcomes	Time in TR: CLAOS 58% ± 4 vs manual 33.7% ± 4.7 $p < 0.01$ SpO2 >95%: 26.5% vs 54.8%, average SpO2: 89.8% vs 92.2% average FiO2: 37% vs 44.1% Manual interventions 0 vs 80 ($p < 0.05$)	No involvement of the sponsors in study design, collection or analysis
Urschitz et al. (2004) Germany	CLAC	Randomised cross-over study	N = 12 GA 25.5 (24–33) weeks PNA 20.5 (4–78) days	NCPAP	Time in TR 87–96%	Descriptive statistics for demographics. ANOVA and Dunnett's & Wilcoxon test	Time in TR: CLAOS 90.5% (59–99.4) vs Manual 81.7% (39–99.8), P = 0.01	Supported by University & Massimo

Legend: PNA-postnatal age; GA-gestational age; HFNC-high flow nasal cannula; NCPAP-nasal continuous positive airway pressure; TR-target range.

Urschitz et al. (2004) and Plottier et al. (2016) used algorithms that were similar in function and execution of FiO_2 changes and as a consequence achieved a similar high percent of time in target (90.5% and 78% respectively). Urschitz et al. (2004) showed a closer relationship between automated and manual achievement to target than Plottier et al. (2016), and when these researchers adjusted their target range the difference between automated and manual control was much reduced. The authors suggested that the width of the SpO_2 target range may affect the effectiveness of the automated system for FiO_2 control.

4. Discussion

This systematic review presents a narrative synthesis of data on oxygen titration control of preterm neonates receiving non-invasive respiratory support and supplemental oxygen. During the automated control, regardless of algorithm type or oxygen target range, neonates spent more time within the target range with reduced overall time outside when compared to manual control. These findings are supported by previous research which assessed the use of CLAOS with invasive ventilation or mixed invasive and non-invasive modalities (Mitre et al., 2018; Claure and Bancalari, 2013; van Kaam et al., 2015; Van Zanten et al., 2017; Sturrock et al., 2020).

Whilst this review demonstrates that CLAOS improves SpO_2 targeting in preterm neonates, the quality of data is low to moderate thus the findings require cautious consideration. However, the age of participants and focus on non-invasive ventilation modalities makes this a different population to those included in NeOProm and other existing studies of automated oxygen titration used with invasive/mixed ventilation modalities. This study contributes a different focus to the existing evidence base.

While automated oxygen systems work well in maintaining an infant within a SpO_2 target range limitations the use of technology, and patient safety concerns, should be explored. Current algorithms are predetermined to respond to oxygen saturation alone but respiratory instability may be an early symptom of other developing conditions. Automation titrating oxygen to prevent desaturation may mask early warning signs of concurrent disease and in so doing exchange one risk for another. A recommendation would be controller systems that simultaneously take into consideration multiple physiological parameters to mitigate against this masking.

Manual overriding of the closed loop automated system to alter the level of FiO_2 is available as a safety precaution. Sturrock et al.' (2020) review noted that manual changes were required by attending practitioners suggesting that unsafe alterations of FiO_2 do occur. Furthermore, saturation probe displacement can occur in response to the neonate moving potentially resulting in lower oxygenation concentration being recorded. Computer systems vary in their specificity to be able to distinguish movement artifacts and saturation probe size can affect reliability of readout (Dargaville et al., 2019). In view of these limitations of automated system there remains the need for nursing oversight of the inspired oxygen concentration and the neonate's condition. Further consideration is required to ensure patient safety is maintained before CLAOS is introduced into routine clinical practice (Mitra et al., 2021).

There is limited data available on adverse effects of the closed loop automated system or on long term clinical outcomes of infants managed exclusively on this modality (Sturrock et al., 2020). Additionally, the potential of closed automated control reducing nursing workload has

not been explored. These are areas which should be the focus of future research.

4.1. Strengths and limitations

A limitation of this review is that meta-analysis was not possible due to the heterogeneity of the studies. Differences in study methodology, algorithm performance and in the reporting of observed outcomes were present. Gestational age at birth was variable as was timing of the intervention. Whilst time related effects are minimised with the within-subject design, it does make comparisons across studies difficult because of inherent instability at these gestational and actual ages at time of measurement. In addition, the ability to generalise the findings to the intended neonatal population is restricted by the lack of detailed participant data. Only one study (Zapata et al., 2014) reported eligibility denominator data.

Furthermore, a limitation includes the use of a single researcher but involving librarian support and the academic supervisor in the search strategy and review of included studies adds reliability to the findings and recommendations made. The search only covered research published in English, and no grey literature was searched, which risks omitting relevant studies. Despite these limitations a systematic approach has been adopted, aiming to maintain transparency throughout.

5. Conclusions

Supplemental oxygen is an important strategy for the prevention of hypoxic injury in preterm infants. However, unless judicious use is employed, there is a risk for hyperoxic injury to occur. Justification for the use of closed loop automated oxygen systems is based around the desire to minimise oxidative injury and its ensuing morbidities by reducing the variability and challenges of manual control. Manually adjusting and responding to oxygen saturation fluctuations also incurs a high nursing workload. Automated oxygen control has been shown to reduce time outside SpO_2 target range but whether this translates to a reduction in neonatal morbidity and the demands on already stretched nursing capacity is yet to be determined. A multicentre randomised controlled trial to assess long-term outcomes is recommended.

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