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Automated Adjustment of the Fraction of Inspired Oxygen (FiO_2) and the Time Spent in Normoxemia in Preterm Infants

O Ajuste Automático da Fração Inspirada de Oxigénio (FiO_2) e o Tempo em Normoxémia em Recém-Nascidos Prematuros

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ABSTRACT

Introduction: The challenge of maintaining normoxemia in preterm infants undergoing respiratory support and oxygen therapy has led to the development of closed-loop automatic control systems for FiO_2. The aim of this study was to assess the effectiveness of these systems in maintaining SpO_2 within a target range (90% - 94%) in preterm neonates receiving supplemental oxygen.

Methods: We conducted a single-centre prospective study over a three-year period (2020 - 2023) including preterm infants with a gestational age < 33 weeks who received supplemental oxygen within the first 24 hours of life and either invasive or non-invasive respiratory support. The closed-loop automatic control of FiO_2 used was the Predictive Intelligent Control of Oxygenation feature on Fabian® ventilators. Two groups were randomized and compared, one receiving automatic plus manual control of FiO_2, and the other receiving routine manual control. Uni- and multivariable regression analyses (linear or Poisson) were used to evaluate the association between the use of closed-loop automatic control of FiO_2 and the parameters of manual adjustments, hypoxemia, hyperoxemia, and normoxemia.

Results: The study included 89 patients, of which 45 received automatic plus manual control of FiO_2 and 44 received routine manual control. The first group required fewer manual adjustments of FiO_2, experienced fewer episodes of hypoxemia and hyperoxemia ($p < 0.002$), and spent more time with SpO_2 within the target range ($p < 0.001$), compared to the second group. After adjustment for confounding, the total time spent in normoxemia was higher when in automatic plus manual control of FiO_2 (β = 81.5; 95%CI: 47.9 - 115.2, $p < 0.001$).

Conclusion: The use of closed-loop automatic control of FiO_2 seems feasible and was associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions.

Keywords: Infant, Premature; Hyperoxia; Hypoxia; Oxygen Inhalation Therapy

RESUMO

Introdução: O desafio de manter a normoxemia em recém-nascidos pré-termo submetidos a suporte respiratório e terapia com oxigénio levou ao desenvolvimento de sistemas de controlo automático em circuito fechado para a FiO_2. O objetivo deste estudo foi avaliar a eficácia destes sistemas na manutenção da SpO_2 dentro de uma faixa alvo (90% - 94%) em recém-nascidos pré-termo sob oxigénio suplementar.

Métodos: Conduzimos um estudo prospetivo unicêntrico ao longo de um período de três anos (2020 - 2023) incluindo recém-nascidos pré-termo com idade gestacional < 33 semanas que receberam oxigénio suplementar nas primeiras 24 horas de vida e suporte respiratório invasivo ou não invasivo. O dispositivo de controlo automático em circuito fechado da FiO_2 utilizado foi o Controlo Inteligente Preditivo da Oxigenação nos ventiladores Fabian®. Foram aleatorizados e comparados dois grupos, um que beneficiou do controlo automático mais manual da FiO_2 e outro que recebeu apenas controlo manual de rotina. A análise de regressão (linear ou de Poisson) uni- e multivariada avaliou a associação entre a utilização do controlo automático em circuito fechado da FiO_2 e os parâmetros de ajustes manuais, hipoxemia, hiperoxemia e normoxemia.

Resultados: Foram incluídos 89 pacientes, 45 receberam controlo automático em circuito fechado da FiO_2 e 44 receberam controlo manual de rotina. O primeiro grupo necessitou de menos ajustes manuais da FiO_2, apresentou menor número de episódios de hipoxemia e hiperoxemia ($p < 0,002$), e passou mais tempo com a SpO_2 dentro da faixa alvo ($p < 0,001$), em comparação com o segundo grupo. Após ajuste para variáveis de confundimento, o tempo total em normoxemia demonstrou uma associação significativa com o controlo automático em circuito fechado da FiO_2 (β = 81,5; IC95%: 47,9 - 115,2; $p < 0,001$).

Conclusão: O uso do controlo automático em circuito fechado da FiO_2 parece ser viável e estava associado a um menor número de episódios de hipóxia e hiperóxia, mantendo assim a SpO_2 dentro dos limites normais por períodos mais longos. Além disso, associou-se a uma redução do número de intervenções manuais.

Palavras-chave: Hiperoxemia; Hipoxemia; Oxigenoterapia; Recém-Nascido Prematuro

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KEY MESSAGES

- Maintaining normoxemia in preterm infants undergoing oxygen therapy presents a challenge, as their SpO_2 levels frequently fluctuate, spending extended periods within ranges classified as hypoxemia and hyperoxemia.
- The challenge of maintaining normoxemia has prompted the development of closed-loop automatic control (CLAC) systems for FiO_2.
- This prospective study assessed the effectiveness of CLAC of FiO_2, using the Predictive Intelligent Control of Oxygenation (PRICO) feature on Fabian® ventilators, in maintaining SpO_2 within a target range (90% - 94%) in preterm neonates receiving supplemental oxygen.
- Our results revealed that the use of CLAC of FiO_2 is feasible and is associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions performed by nurses.

INTRODUCTION

Preterm infants of very low and extremely low birth weight at birth, due to their neurological and lung immaturity, require respiratory support and supplemental oxygen postnatally in order to maintain adequate peripheral oxygen saturation (SpO_2), as assessed by pulse oximetry. Maintaining normoxemia presents a challenge, as the SpO_2 levels of infants undergoing oxygen therapy frequently fluctuate, spending extended periods within ranges classified as hypoxemia and hyperoxemia. These conditions are associated with an increased risk of mortality and retinopathy of prematurity (ROP), respectively, underscoring the critical importance of maintaining appropriate oxygen saturation levels in this vulnerable population.[1,2]

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome (RDS) recommend maintaining the SpO_2 target between 90% and 94% for preterm infants receiving oxygen therapy.[3] Additionally, ventilator alarm limits should be set between 89% and 95%.[3] Intermittent hypoxemic episodes in preterm infants can result from worsening of the RDS, recurrent apnea, and active exhalation during mechanical ventilation.[4] Periods of hyperoxia often occur due to inadequate adjustment of the FiO_2 and may vary in duration. The challenge of maintaining normoxemia has prompted the development of closed-loop automatic control (CLAC) systems for FiO_2. These systems involve algorithms that use the patient's SpO_2 level to regulate the delivery of FiO_2 by the ventilator, thereby ensuring that SpO_2 remains within the desired range. Additionally, such automatic control systems alleviate the workload of nurses.

The primary objective of this study was to assess the effectiveness of CLAC of FiO_2 using the Predictive Intelligent Control of Oxygenation (PRICO) feature on Fabian® ventilators in maintaining SpO_2 within a target range in preterm neonates receiving supplemental oxygen, by measuring the time in minutes spent in normoxemia.

METHODS

This study was conducted prospectively over a three-year period (2020 - 2023) in a tertiary university neonatal intensive care unit (NICU), following authorization from the local ethics committee.

Preterm infants born with a gestational age of less than 33 weeks who required supplemental oxygen and either invasive or non-invasive respiratory support within the first 24 hours of life were included in the study. Infants affected by major congenital anomalies, chromosomal anomalies, those with hemodynamic instability, and those whose parents/guardians did not authorize participation in the study after explanation and request for informed consent were excluded.

The infants were sequentially included in the study based on the order of birth and were randomized 1:1 into two groups: one receiving automatic plus manual control (A+MC) of FiO_2, and the other receiving routine manual control (RMC) only. Randomization was based on a predetermined list created using the patient's inclusion number in the study, which corresponded to the group in which the patient was placed. This placement alternated between the two groups. The doctor who included the patient in the study had access to the predetermined list. Peripheral oxygen saturation was continuously monitored on the NICU monitor as per standard protocol, and a second oximetry sensor was placed for PRICO input in the neonates randomized to receive A+MC of FiO_2. Due to the nature of the intervention, it was not feasible to blind the study nurses and doctors. The manual control of FiO_2 was conducted by the responsible nurse after receiving the necessary information to participate in the study and maintain the FiO_2 at a target SpO_2 of 90% - 94%. Whenever nurses made a manual adjustment of FiO_2, they were required to record on a recording sheet the patient's SpO_2 and FiO_2 at that moment, along with the hour and minute of the adjustment, and the reason for the manual adjustment. During manipulations and

procedures performed on the neonates, the typical increases in FiO_2 and its control during the procedure were not recorded. The registration was conducted only during the first 24 hours of life. At 24 hours of life, registration was discontinued, and the children were then followed with standard treatment. Following our national practice, the nurse-to-patient ratio was 1:2.

The infants who underwent A+MC of FiO_2 used the PRICO feature on the Fabian® ventilator. Children who only used RMC did not benefit from automatic control technology, remaining solely reliant on manual adjustments made by the nurse in charge. The ventilators used in this study were the Fabian HFO® (Acutronic, Hirzel, Switzerland), equipped with PRICO technology. SpO_2 was assessed using the Radical Masimo® system (Masimo, Irvine, California, USA) with an average time of 8 seconds. The PRICO algorithm of the Fabian ventilator is a rule-based control scheme with proportion-integral-derivative characteristics that uses both the current SpO_2 and the trend SpO_2 measurement as inputs.[5,6] Detailed information on the algorithm is provided in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22397/15695). As the Fabian® ventilator requires SpO_2 input from a separate Masimo pulse oximeter, a second pulse oximeter was attached to the patient throughout the entire study period. Both pulse oximeters were placed in a post-ductal site.

To compare the two groups of infants in this study, we collected data on the following variables: mother's age, diseases and habits, pregnancy complications, use of antenatal corticosteroids and neuroprotection with magnesium sulphate, delivery mode, resuscitation maneuvers and Apgar scores, demographics, neonatal morbidities, including respiratory distress syndrome (RDS), pneumothorax, pneumonia, bronchopulmonary dysplasia (BPD, considered in this study oxygen dependency or ventilatory support at 36 weeks), hemodynamically significant patent ductus arteriosus (HS-PDA), early and late sepsis, meningitis, necrotizing enterocolitis (NEC), intra-ventricular hemorrhage (IVH), periventricular infarction (PVI), cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP), mortality, and length of NICU stay. This comprehensive set of data allowed for a thorough comparison between the two groups of infants in the study. Additionally, we gathered data on treatments, including surfactant administration, invasive mechanical ventilation, use of supplemental oxygen, oxygen requirement at discharge, medications (such as inhaled corticosteroids, bronchodilators and diuretics), duration of total parenteral nutrition (TPN), surgical closure of HS-PDA and placement of a ventriculoperitoneal shunt. The definitions and criteria used in the diagnosis of the mentioned conditions have been recently described.[7]

The resuscitation guidelines used were those from the Portuguese Society of Neonatology (available at www.lusoneonatologia.com), which have been updated in accordance with the European Resuscitation Council guidelines.[8] The ventilation practices used were as follows: non-invasive ventilation (NCPAP) was the preferred mode of ventilation in preterm infants with respiratory drive. Synchronized intermittent positive pressure ventilation (SIPPV) associated with volume guarantee (VG) was employed in cases of NCPAP failure or in preterm infants without respiratory drive. High frequency oscillatory ventilation (HFOV) at our center is typically employed as a rescue ventilation strategy. The strategy of permissive hypercapnia was advocated. Caffeine citrate was routinely administered from day one of life, regardless of apneas, until the infant reached 34 weeks of gestational age.

The primary outcome measured was the percentage of time spent within the target SpO_2 range. Additionally, a comparison was conducted for the number of FiO_2 adjustments between the two groups of children, with and without automatic FiO_2 control, and whether these adjustments were made in response to hypoxemia or hyperoxemia.

Statistics

Data collection and statistical analysis were performed using IBM SPSS® statistics 29.

Categorical variables were described using absolute and relative frequencies. Continuous variables with symmetric distribution were described using mean (± standard deviation), while continuous variables with asymmetric distribution were described using median (minimum-maximum). Chi-square or Fisher's exact test were applied to compare categorical variables, while independent t-test and Mann-Whitney U test were used for symmetric and asymmetric continuous variables, respectively. Poisson regression models were used to analyze count-based outcomes: total number of manual FiO_2 adjustments (Model 1), the number of hypoxemic episodes (Model 2), and the number of hyperoxemic episodes (Model 5). Results from Poisson regression were reported as incidence rate ratios (IRR) with 95% confidence intervals (CIs). For continuous outcomes, linear regression models were applied to evaluate total time spent in hypoxemia (Model 3), percentage of time below the target range (Model 4), total time in hyperoxemia (Model 6), percentage of time above the target range (Model 7), total time in normoxemia (Model 8), and percentage of time within the target range (Model 9). Results from linear regression were expressed as beta-coefficients (β) with 95% CIs. Multivariable models were adjusted for gestational age and birth weight to control for potential confounding factors. A p-value < 0.05 was considered statistically significant.

RESULTS

Over the course of the three-year study, a total of 89 patients were enrolled. Out of these patients, 45 received A+MC of FiO_2 within the first 24 hours of life, while 44 received CMR. Maternal and obstetrical data, delivery room management, as well as neonatal morbidity and mortality of both groups, are reported and compared in Table 1. The mean gestational age was higher in the A+MC of FiO_2 group

Table 1 – Maternal and obstetrical data, delivery room management, and neonatal morbidity and mortality of infants according to type (automated + manual *versus* routine manual) of FiO_2 control in the first 24 hours of life (part 1 of 2)

	Total (n = 89)	**A+MC of FiO_2** (n = 45)	**RMC of FiO_2** (n = 44)	***p*-value**
Maternal and obstetrical data				
Mother's age, mean (± SD)	31.79 (± 6.1)	32.1 (± 6.2)	31.4 (± 6.0)	0.612Ω
1st pregnancy, n (%)	43 (48.3)	23 (51.1)	20 (45.5)	0.593*
Multiple gestation, n (%)	20 (22.5)	10 (22.2)	10 (22.7)	0.954*
Antenatal steroids, n (%)	84 (94.4)	43 (95.6)	41 (93.2)	0.367**
- Full cycle, n (%)	61 (68.5)	33 (76.7)	28 (68.3)	0.325*
Neuroprotection ($MgSO_4$), n (%)	71 (79.8)	37 (82.2)	34 (77.3)	0.561*
Chronic diseases, n (%)	28 (31.5)	14 (31.1)	14 (31.8)	0.943*
Chronic arterial hypertension, n (%	6 (6.7)	4 (8.9)	2 (4.5)	0.677**
Gestational hypertension, n (%)	0	0	0	-
Preeclampsia/Eclampsia, n (%)	19 (21.3)	12 (26.7)	7 (15.9)	0.216*
HEELP syndrome, n (%)	0	0	0	-
DM 1, n (%)	1 (1.1)	1 (2.2)	0	0.999**
Placenta abruption, n (%)	3 (3.4)	2 (4.4)	1(2.3)	0.434**
Gestational diabetes, n (%)	11 (12.4)	9 (20)	2 (4.5)	0.050**
Fetal growth restriction, n (%)	18 (20.2)	8 (17.8)	10 (22.7)	0.561*
Rupture of membranes > 18h, n (%)	14 (15.7)	8 (17.8)	6 (13.6)	0.592*
Clinical chorioamnionitis, n (%)	13 (14.6)	5 (11.1)	8 (18.2)	0.345*
Histopathological chorioamnionitis, n (%)	20 (22.5)	8 (17.8)	12 (27.3)	0.283*
Smoking, n (%)	7 (7.9)	4 (8.9)	3 (6.8)	0.899**
Alcohol, n (%)	0	0	0	-
Drugs, n (%)	0	0	0	-
Delivery room management				
C-section, n (%)	63 (70.1)	32 (71.1)	31 (70.5)	0.946*
Male, n (%)	47 (52.8)	22 (48.9)	25 (56.8)	0.454*
Gestational age, mean (± SD)	28.8 (± 2.3)	29.4 (± 2.2)	28.2 (± 2.4)	**0.022**Ω
Birthweight, mean (± SD)	1222.2 (± 417.9)	1311 (± 458)	1131 (± 355)	**0.042**Ω
Positive pressure ventilation, n (%)	76 (85.4)	39 (86.7)	37 (84.1)	0.731*
ETT + MV, n (%)	35 (39.3)	16 (35.6)	19 (43.2)	0.461*
Early NCPAP, n (%)	55 (61.8)	31 (68.9)	24 (54.5)	0.164*
Oxygen, n (%)*	89 (100)	45 (100)	44 (100)	0.999**
Adrenaline, n (%)	3 (3.4)	2 (4.4)	1 (2.3)	0.999**
Apgar score				
≤ 5 at 1st minute, n (%)	22 (24.7)	9 (20)	13 (29.5)	0.297*
≤ 5 at 5th minutes, n (%)	3 (3.4)	2 (4.4)	1 (2.3)	0.999**

BPD: bronchopulmonary dysplasia; cLPV: cystic periventricular leukomalacia; DM: diabetes melitus; ETT + MV: endotracheal tube + mechanical ventilation; HELLP: hemolysis, elevated liver enzymes and low platelet count; HS-PDA: hemodynamically significant patent ductus arteriosus; IMV: invasive mechanical ventilation; IVH: intraventricular haemorrhage; n: number; NCPAP: nasal continuous distending pressure; NEC: necrotizing enterocolitis; O_2: oxygen; PDA: patent ductus arteriosus; PVI: periventricular venous infarction; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SD: standard deviation; TPN: total parenteral nutrition;
bold *p*: significant value; **Ω**: Independent *t* test; **ΩΩ**: Mann Whitney U test; *: Chi square test; **: Fisher's exact test.

(29.4 ± 2.2 weeks *vs* 28.2 ± 2.4 weeks, $p = 0.022$), as well as the mean birthweight (1311 ± 458 g *vs* 1131 ± 355 g, $p = 0.042$). No differences were observed in obstetric, delivery, and neonatal morbidity and mortality between the two groups. Infants in the A+MC of FiO_2 group required fewer manual adjustments of FiO_2 ($p < 0.001$), experienced fewer episodes of hypoxemia ($p < 0.001$) and hyperoxemia ($p < 0.001$), and spent more time with SpO_2 within the target range of 90% - 94% ($p < 0.001$) compared to those in the MC of FiO_2 group, as shown in Table 2. On the contrary, in the group of children receiving only routine manual FiO_2 control, a higher number of FiO_2 adjustments were needed ($p < 0.001$).

Uni- and multivariable analysis for strategies of control for FiO_2 is reported in Table 3. Total number of manual FiO_2 adjustments [IRR (95% CI) = 0.08 (0.05; 0.14)], number of hypoxemic episodes [IRR = 0.16 (0.09; 0.27)], total time in hypoxemia [β (95% CI) = -9.0 (-13.2; -4.9)], percentage of time below target range [β = -0.62 (-0.9; -0.3)], total time in hyperoxemia [β = -72.6 (-106.7; 40.8)], and percentage of time above target range [β = -4.7 (-7.0; -2.4)], were significantly associated with strategies of FiO_2 control, in the univariate analysis (all $p < 0.001$). The A+MC group also showed a significant increase in total time spent in normoxemia [β = 82.8 (49.2 - 116.3)], which remained significant in the adjusted analysis [β = 81.5 (47.9 - 115.2)] ($p < 0.001$).

DISCUSSION

Newborn preterm infants with respiratory disease often need extra oxygen, but it must be administered carefully to prevent the harmful effects of both low oxygen levels (hypoxia) and high oxygen levels (hyperoxia).[9] The manual adjustment of FiO_2 is known to result in a significant amount of time spent outside the target SpO_2 range.[10] Closed-loop

Table 1 – Maternal and obstetrical data, delivery room management, and neonatal morbidity and mortality of infants according to type (automated + manual *versus* routine manual) of FiO_2 control in the first 24 hours of life (part 2 of 2)

	Total (n = 89)	**A+MC of FiO_2** (n = 45)	**RMC of FiO_2** (n = 44)	***p*-value**
Neonatal morbidity and mortality				
RDS, n (%)	89 (100)	45 (100)	44 (100)	0.999**
Surfactant, n (%)	56 (62.9)	32 (71.1)	24 (54.5)	0.106*
BPD (O_2 at 36 weeks), n (%)	11 (12.4)	5 (11.1)	6 (13.6)	0.717*
IMV, n (%) Days of IMV, median (min - max)	25 (2-93)	45 (100) 25 (5-69)	44 (100) 25.5 (2 - 93)	0.999** 0.977ΩΩ
NCPAP, n (%)	80 (89.9)	40 (88.9)	40 (90.9)	0.752*
Days on CPAP, median (min - max)	22 (2 - 72)	21.5 (2 - 55)	23 (2 - 72)	0.937ΩΩ
Days with O_2 supplementation, median (min - max)	8 (1 - 95)	7 (2 - 80)	15 (1 - 95)	0.199ΩΩ
Need of O_2 at discharge, n (%)	1 (1.1)	1 (2.2)	0	0.989**
Days with PTN, median (min - max)	14 (4 - 107)	17 (5 - 76)	14 (4 - 107)	0.232ΩΩ
HS-PDA, n (%)	24 (27)	14 (31.1)	10 (22.7)	0.373*
PDA surgical closure, n (%)	3 (3.4)	2 (14.3)	1 (10)	0.999**
NEC stage ≥ 2, n (%)	4 (4.5)	2 (4.4)	2 (4.5)	0.999**
IHV stage 3, n (%)	15 (16.9	8 (17.8)	7 (15.9)	0.814*
PVI, n (%)	7 (7.9)	4 (8.9)	3 (6.8)	0.889**
cPVL, n (%)	5 (5.6)	4 (8.9)	1 (2.3)	0.361**
ROP stage > 2, n (%)	10 (11.2)	6 (13.3)	4 (9.1)	0.526*
Early-onset sepsis, n (%)	8 (9)	4 (8.9)	4 (9.1)	0.988**
Late-onset sepsis, n (%)	27 (30.3)	14 (31.1)	13 (29.5)	0.872*
Pneumonia, n (%)	11 (12.4)	5 (11.1)	6 (13.6)	0.717*
Meningitis, n (%)	1 (1.1)	1 (2.2)	0	0.999**
Days in NICU, median (min - max)	52 (17-111)	51.5 (17-105)	55 (20 - 111)	0.818ΩΩ
Deceased, n (%)	10 (11.2)	5 (11.1)	5 (11.4)	0.970*

BPD: bronchopulmonary dysplasia; cLPV: cystic periventricular leukomalacia; DM: diabetes melitus; ETT + MV: endotracheal tube + mechanical ventilation; HELLP: hemolysis, elevated liver enzymes and low platelet count; HS-PDA: hemodynamically significant patent ductus arteriosus; IMV: invasive mechanical ventilation; IVH: intraventricular haemorrhage; n: number; NCPAP: nasal continuous distending pressure; NEC: necrotizing enterocolitis; O_2: oxygen; PDA: patent ductus arteriosus; PVI: periventricular venous infarction; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SD: standard deviation; TPN: total parenteral nutrition;
bold *p*: significant value; **Ω**: Independent *t* test; **ΩΩ**: Mann Whitney U test; *: Chi square test; **: Fisher's exact test.

Table 2 – Manual adjustments of FiO_2, hyperoxemia, hypoxemia and time in normoxemia for the two groups automated + manual *versus* routine manual control of FiO_2 in the first 24 hours of life

	A+MC of FiO_2 (n = 45)	RMC of FiO_2 (n = 44)	*p*-value
Total no. of manual FiO_2 adjustments, median (min - max)	0 (0 - 4)	3.5 (0 - 12)	**< 0.001**ΩΩ
≥ 1 manual FiO_2 adjustments, n (%)[a]	10 (22.2)	36 (81.8)	**< 0.001***
HYPOXEMIC EPISODES			
No. of infants with hypoxemic episodes, n (%)	11 (24.0)	31 (70.5)	**< 0.001***
No. of hypoxemic episodes, median (min - max)	0 (0 - 4)	2 (0 - 8)	**< 0.001**ΩΩ
≥ 2 episodes, n (%)[a]	3 (6.7)	24 (54.5)	**< 0.001***
Total time in hypoxemia, median (min - max), minutes	0 (0 - 16)	8 (0 - 80)	**< 0.001**ΩΩ
≥ 8 minutes, n (%)[a]	3 (6.7)	23 (52.3)	**< 0.001***
% of time below target range, median (min - max)	0 (0 - 1.1)	0.6 (0 - 5.5)	**< 0.001**ΩΩ
≥ 1% below, n (%)[a]	1 (2.2)	11 (25.0)	**0.002***
HYPEROXEMIC EPISODES			
Number of infants with hyperoxemic episodes, n (%)	0 (0)	28 (63.6)	**< 0.001***
Nº of hyperoxemic episodes, median (min - max)	0 (0-0)	1 (0 - 6)	**< 0.001**ΩΩ
≥ 1 episodes, n (%)[a]	0 (0)	28 (100)	**< 0.001***
Total time in hyperoxemia, median (min - max), minutes	0 (0 - 0)	25 (0 - 480)	**< 0.001**ΩΩ
≥ 25 minutes, n (%)[a]	0 (0)	28 (100)	**< 0.001***
% of time above target range, median (min - max)	0 (0 - 0)	4.2 (0.3 - 33.3)	**< 0.001**ΩΩ
≥ 4% above, n (%)[a]	2 (4.4)	15 (34.1)	**<0.001***
NORMOXEMIA			
Total time in normoxemia, median (min - max), minutes	1440 (1424 - 1440)	1406 (936 - 1440)	**< 0.001**ΩΩ
% of time in normoxemia, median (min - max)	100 (98.9 - 100)	97.7 (65 - 100)	**0.103**ΩΩ

ΩΩ: Mann Whitney U test; *: Chi-square test; [a]: The cut-offs used to dichotomize the variables were the medians obtained from the manual adjustment parameters for hypoxemia and hyperoxemia, respectively.

automatic control delivery systems, emerging as a potential solution, have demonstrated advantages in crossover studies. They increase the percentage of time infants spend within the target SpO_2 range and reduce the need for manual FiO_2 adjustments in those receiving non-invasive or invasive respiratory support.[11-13] A recent systematic review and meta-analysis by Abdo *et al*, encompassing 13 trials, concluded that CLAC is rapid and effective in controlling infants' SpO_2, and it can help reduce the workload for nurses but should not replace clinical supervision.[14]

According to a survey conducted in the United Kingdom, CLAC systems for FiO_2 are not yet widely used in neonatology units.[15] There are still few studies on the long-term outcomes. In the study by Salverda H *et al*, no differences were found in neurodevelopment at two years of age between preterm infants who used CLAC during the entire period of oxygen therapy and those who did not use it.[16] The true long-term benefits for extreme premature children are also not yet known; however, trials are currently ongoing.[17]

Several algorithms for CLAC exist, with PRICO being the one used by Fabian® ventilators. It has already demonstrated superiority in previous studies, showing its effectiveness in maintaining saturations within the desired limits.[18] In our study, the PRICO algorithm used in preterm infants showed advantages in maintaining saturations within the desired range for longer periods, reducing episodes of hyperoxia and hypoxia, and decreasing the number of adjustments required by nurses. In fact, our study demonstrated a statistically significant association between the use of CLAC and a greater percentage of time spent in normoxemia, even when adjusted to other covariates, thereby reducing the periods above and below the established limits to 94% and 90%, respectively. Additionally, CLAC showed a statistically significant association with a lower number of FiO_2 adjustments made by nurses, thus proving to be a valuable aid in their work.

In our study, we originally intended to include premature children of lower gestational age and weight. However, the timing of patient inclusion coincided with the period of the COVID-19 pandemic, during which our unit experienced a significant decrease in admissions of extreme premature babies. As a result, the included infants had a higher

Table 3 – Unadjusted and adjusted regression analysis of FiO_2 regimens on oxygenation outcomes

	Unadjusted			Adjusted**		
	Coefficient*	95% CI	*p*-value	Coefficient*	95% CI	*p*-value
Model 1						
A+MC	0.08	0.05; 0.14	**< 0.001**	-	-	0.757
RMC	1.0					
Model 2						
A+MC	0.16	0.09; 0.27	**< 0.001**	-	-	0.450
RMC	1.0					
Model 3						
A+MC	-9.0	-13.2; -4.9	**< 0.001**	-	-	0.554
RMC	1.0					
Model 4						
A+MC	-0.62	-0.9; -0.3	**< 0.001**	-	-	0.563
RMC	1.0					
Model 5						
A+MC	-	-	0.832			
RMC						
Model 6						
A+MC	-72.6	-106.7; -40.8	**< 0.001**	-	-	0.065
RMC	1.0					
Model 7						
A+MC	-4.7	-7.0; -2.4	**< 0.001**	-	-	0.095
RMC	1.0					
Model 8						
A+MC	82.8	49.2; 116.3	**< 0.001**	81.5	47.9; 115.2	**< 0.001**
RMC	1.0			1.0		
Model 9						
A+MC	-	-	0.871	-	-	
RMC						

*: Beta-coefficients obtained by linear regression were reported, except in model 1, 2 and 5 which incidence rate ratios (IRR) coefficients were reported, obtained by Poisson regression analysis. **: Adjusted for gestational age and birth weight.
Model 1: Total no. of manual FiO_2 adjustments as dependent variable;
Model 2: No. of hypoxemic episodes as dependent variable;
Model 3: Total time in hypoxemia; Model 4: % of time below target range;
Model 5: No. of hyperoxemic episodes;
Model 6: Total time in hyperoxemia;
Model 7: % of time above target range;
Model 8: Total time in normoxemia;
Model 9: % of time in normoxemia;
-: coefficients not considered because *p*-value > 0.05.

gestational age than initially expected, and this is a limitation of our study. Less premature and consequently more stable infants may derive fewer benefits from CLAC of FiO_2 compared to those who are more premature and less stable. However, we anticipate that our results might be similar to those obtained from a sample of patients with a lower gestational age, as observed in previous studies.[18,19]

The intermittent hypoxia typical of preterm infants is associated with impaired growth, as well as possible longer-term cardiorespiratory instability and poor neurodevelopmental outcome.[20] Hyperoxia has been associated with and development of severe ROP, BPD, and brain injury.[21] Given that hyperoxia is neither natural nor random but rather an unintended consequence of the intervention, it is essential to develop means to prevent the excessive generation of free oxygen radicals and subsequent irreversible damage

to target organs.

While the reduction in nurses' workload associated with the use of CLAC of FiO_2 appears advantageous, it is important to highlight that nursing supervision throughout the shift is essential. Some scenarios may require the nurse's immediate action before the CLAC response time, such as in sudden apneas, or when the automatic control may accidentally end up being turned off.

The results of this study are important because they support the use of CLAC of FiO_2 throughout the entire period of mechanical ventilation with oxygen therapy, not just in the first 24 hours of life. However, there are still areas where this study can be deepened and continued, such as extending the protocol over a longer period and including neurodevelopmental assessments in the medium to long term.

None of the studies conducted to date have investigated whether automated control of FiO_2 can actually improve early and long-term respiratory and neurodevelopmental outcomes in preterm infants. Further large-scale studies are needed to assess the actual clinical relevance of these FiO_2 CLAC devices and to determine whether they should become the standard of care.

In conclusion, our study found that the use of CLAC of FiO_2 is feasible and is associated with fewer episodes of hypoxia and hyperoxia, thereby maintaining SpO_2 within normal limits for longer periods. Additionally, it has been shown to be associated with a reduction in manual interventions performed by nurses.

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AUTHOR CONTRIBUTIONS

GR: Study design, data collection, writing and critical review of the manuscript.

PS: Data collection and critical review of the manuscript.

FFL, RA: Statistical analysis of the data and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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REFERENCES

1. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al; SUPPORT study group of the eunice kennedy shriver nichd neonatal research network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362:1959-69.
2. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al; BOOST II United Kingdom Collaborative Group; BOOST II Australia Collaborative Group; BOOST II New Zealand Collaborative Group. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368:2094-104.
3. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology. 2019;115:432-50.
4. Bolivar JM, Gerhardt T, Gonzalez A, Hummler H, Claure N, Everett R, et al. Mechanisms for episodes of hypoxemia in preterm infants undergoing mechanical ventilation. J Pediatr. 1995;127:767-73.
5. Hütten MC, Goos TG, Ophelders D, Nikiforou M, Kuypers E, Willems M, et al. Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. Pediatr Res. 2015;78:657-63.
6. Dijkman KP, Mohns T, Dieleman JP, van Pul C, Goos TG, Reiss IK, et al. Predictive intelligent control of oxygenation (PRICO) in preterm infants on high flow nasal cannula support: a randomised cross-over study. Arch Dis Child Fetal Neonatal E. 2021;106:621-6.
7. Rocha G, de Lima FF, Machado AP, Guimarães H; Collaborators of the hypertensive disorders of pregnancy study group. Preeclampsia predicts higher incidence of bronchopulmonary dysplasia. J Perinatol. 2018;38:1165-73.
8. Madar J, Roehr CC, Ainsworth S, Ersdal H, Morley C, Rüdiger M, et al. European resuscitation council guidelines 2021: newborn resuscitation and support of transition of infants at birth. Resuscitation. 2021;161:291-326.
9. Dargaville PA, Marshall AP, McLeod L, Salverda HH, Te Pas AB, Gale

TJ. Automation of oxygen titration in preterm infants: current evidence and future challenges. Early Hum Dev. 2021;162:105462.
10. Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, et al; AVIOx Study Group. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. Pediatrics. 2006;118:1574-82.
11. Dani C. Automated control of inspired oxygen (FiO_2) in preterm infants: literature review. Pediatr Pulmonol. 2019;54:358-63.
12. Sturrock S, Ambulkar H, Williams EE, Sweeney S, Bednarczuk NF, Dassios T, et al. A randomised crossover trial of closed loop automated oxygen control in preterm, ventilated infants. Acta Paediatr. 2021;110:833-7.
13. Sturrock S, Williams E, Dassios T, Greenough A. Closed loop automated oxygen control in neonates-a review. Acta Paediatr. 2020;109:914-22.
14. Abdo M, Hanbal A, Asla MM, Ishqair A, Alfar M, Elnaiem W, et al. Automated versus manual oxygen control in preterm infants receiving respiratory support: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2022;35:6069-76.
15. Kaltsogianni O, Dassios T, Belbal R, Greenough A. Survey of closed-loop automated oxygen control systems in neonatal intensive care units. Acta Paediatr. 2022;111:1002-3.
16. Salverda HH, Oldenburger NN, Rijken M, Tan RR, Pas AB, van Klink JM. Automated oxygen control for very preterm infants and neurodevelopmental outcome at 2 years-a retrospective cohort study. Eur J Pediatr. 2023;182:1593-9.
17. Maiwald CA, Niemarkt HJ, Poets CF, Urschitz MS, König J, Hummler H, et al. Effects of closed-loop automatic control of the inspiratory fraction of oxygen (FiO_2-C) on outcome of extremely preterm infants - study protocol of a randomized controlled parallel group multicenter trial for safety and efficacy. BMC Pediatr. 2019;19:363.
18. Dijkman KP, Goos TG, Dieleman JP, Mohns T, van Pul C, Andriessen P, et al. Predictive intelligent control of oxygenation in preterm infants: a two-center feasibility study. Neonatology. 2023;120:235-41.
19. van Kaam AH, Hummler HD, Wilinska M, Swietlinski J, Lal MK, te Pas AB, et al. Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. J Pediatr. 2015;167:545-50.e1-2.
20. Martin RJ, Wang K, Köroğlu O, Di Fiore J, Kc P. Intermittent hypoxic episodes in preterm infants: do they matter? Neonatology. 2011;100:303-10.
21. Deuber C, Terhaar M. Hyperoxia in very preterm infants: a systematic review of the literature. J Perinat Neonatal Nurs. 2011;25:268-74.