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Performance and safety of the PRICO closed-loop oxygen saturation targeting system in neonates: pragmatic multicentre cross-over study (TarOx Study)

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ABSTRACT

Objective This study aims to evaluate the performance of the fabian-Predictive-Intelligent-Control-of-Oxygenation (PRICO) system for automated control of the fraction of inspired oxygen (FiO_2).

Design Multicentre randomised cross-over study.

Setting Five neonatal intensive care units experienced with automated control of FiO_2 and the fabian ventilator.

Patients 39 infants: median gestational age of 27 weeks (IQR: 26–30), postnatal age 7 days (IQR: 2–17), weight 1120 g (IQR: 915–1588), FiO_2 0.32 (IQR: 0.22–0.43) receiving both non-invasive (27) and invasive (12) respiratory support.

Intervention Randomised sequential 24-hour periods of automated and manual FiO_2 control.

Main outcome measures Proportion (%) of time in normoxaemia (90%–95% with FiO_2>0.21 and 90%–100% when FiO_2=0.21) was the primary endpoint. Secondary endpoints were severe hypoxaemia (<80%) and severe hyperoxaemia (>98% with FiO_2>0.21) and prevalence of episodes ≥60 s at these two SpO_2 extremes.

Results During automated control, subjects spent more time in normoxaemia (74%±22% vs 51%±22%, p<0.001) with less time above and below (<90% (9%±8% vs 12%±11%, p<0.001) and >95% with FiO_2>0.21 (16%±19% vs 35%±24%) p<0.001). They spent less time in severe hyperoxaemia (1% (0%–3.5%) vs 5% (1%–10%), p<0.001) but exposure to severe hypoxaemia was low in both arms and not different. The differences in prolonged episodes of SpO_2 were consistent with the times at extremes.

Conclusions This study demonstrates the ability of the PRICO automated oxygen control algorithm to improve the maintenance of SpO_2 in normoxaemia and to avoid hyperoxaemia without increasing hypoxaemia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Oxygenation targeting in newborn infants is essential but successful manual titration of oxygen is challenging.

⇒ Automated control of inspired oxygen is now available and shows great promise, but efficacy and safety may vary between the different available algorithms.

WHAT THIS STUDY ADDS

⇒ In a multicentre study, the fabian-Predictive-Intelligent-Control-of-Oxygenation (PRICO) automated system was shown to be effective and safe in neonates of different maturities among a range of ventilator modalities.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on this and other smaller studies, the fabian-PRICO can be routinely used in clinical practice.

⇒ Additional research is indicated to evaluate automated oxygen control systems to not only determine how they can be improved but also how their use can be optimised in different clinical environments.

BACKGROUND

Respiratory instability leading to frequent hypoxaemic episodes is a common problem in preterm infants. Therefore, the SpO_2 is continuously monitored, aiming to keep it within a target range by manually adjusting the fraction of inspired oxygen (FiO_2).[1] However, nurses struggle with this task, and as a result, hyperoxaemia and hypoxaemia are prevalent.[2 3] Both are associated with adverse outcomes in preterm infants.[4–8] Improving oxygen targeting in preterm infants is, therefore, needed.

Modern neonatal ventilators offer the option of automated closed-loop oxygen control (A-FiO_2). During A-FiO_2, a software algorithm

adjusts the delivered FiO_2 based on the measured SpO_2 and the set target range. Many studies have reported that A-FiO_2, compared with manual control (M-FiO_2), improves the time spent within the target range and reduces the exposure to hypoxaemia and/or hyperoxaemia.[9 10] However, A-FiO_2 control algorithms differ considerably,[11] and therefore, the performance of each algorithm needs to be studied under different conditions before conclusions can be drawn on its relative effectiveness and limitations. The Predictive-Intelligent-Control-of-Oxygenation (PRICO) A-FiO_2 algorithm, introduced in 2016, had only been evaluated in two small single-centre studies.[12 13] Therefore, the aim of this study was to evaluate the efficacy and safety of the PRICO algorithm in a wide range of infants supported with different modes of respiratory support, across multiple centres.

METHODS

This was a multicentre randomised cross-over study in five European neonatal intensive care unit (NICUs), one in the Netherlands and four in Poland. Potential sites were only considered if they had experience with the fabian ventilator (Vyaire Medical, Mettawa, USA) and A-FiO_2. The study was sponsored by Vyaire and designed as a postmarket clinical follow-up study conducted to fulfil the EU Medical Device Regulations and registered at ClinicalTrials.gov (NCT 04957472). There was no patient or public involvement in designing the study. An independent data safety monitoring committee conducted interim safety reviews masked to the sponsor and the investigators. A contract research organisation managed the study activities including site monitoring and collection of adverse events. This is an independent report from the investigators, which was neither commissioned nor influenced by the sponsor.

A-FiO_2 system

The PRICO A-FiO_2 option of the fabian ventilator is available for all invasive and non-invasive respiratory support modalities. PRICO uses a rule-based algorithm, first described by Hütten *et al*.[14] It monitors the SpO_2 every second using an integrated Masimo pulse oximeter (Masimo Corporation, California, USA). Based on a weighted average of these data, an adjustment in FiO_2 is made every 30 s, if warranted. When within the set SpO_2 target range, the FiO_2 adjustment is ±1% towards the midpoint. When outside the target range the adjustment varies (±1%–10%), based on a proprietary algorithm that takes into account the depth and the trajectory of the predicted response to a change in oxygen. In certain conditions (no SpO_2 reading (drop-out) or exceeding operator set parameters) the system switches off automated control and falls back to manual control at the FiO_2 previously set by the clinician, while generating an alarm. The system returns to A-FiO_2 control when the condition resolves or after manual reactivation.

Study population

Infants in the NICU needing a target of 90%–95% SpO_2, regardless of weight or gestational age, were eligible for enrolment if they required invasive or non-invasive respiratory support and supplemental oxygen (>0.21). Infants were excluded if they had congenital anomalies or uncontrolled haemodynamic instability. In addition, infants were also excluded if the attending physician did not believe participation was in the best interest of the infant, or if parental consent was not obtained.

Study protocol

Subjects, a sample of convenience, were assigned to sequential 24-hour periods of A-FiO_2 and M-FiO_2 control in random order. Except for the order of intervention, all other aspects of care, including all PRICO settings (oximeter averaging, SpO_2 alarm levels and target range thresholds), were according to each unit's standard practice. For infants ready to start caffeine therapy, entry was delayed at least 12 hours to avoid caffeine wash-in effects. Subjects exited the study early if they required a change in the mode of respiratory support, or if the attending physician or the parents withdrew support for participation.

An electronic web-based system (CastorEDC, Amsterdam, Netherlands) was used for the collection of baseline characteristics and subject randomisation. The SpO_2 values and ventilator settings were recorded on a laptop computer attached to ventilator during both arms of the study. These data were uploaded to the sponsor's study portal and automatically incorporated into a database. The analyses were based on 4 s data points. Remote monitoring reports were automatically generated and sent to the study monitor after each enrolment, with potential inconsistencies adjudicated. Periodic site visits also audited study conduct.

Endpoints

The proportion of time in normoxaemia was the primary endpoint and specified as SpO_2 90%–95% with FiO_2>0.21, plus time 90%–100% with FiO_2=0.21).[9 15] Avoiding SpO_2 extremes associated with severe hypoxaemia (<80%)[5 16] and severe hyperoxaemia (>98% with FiO_2>0.21)[15 16] were also specified outcomes.

Other descriptive endpoints were (1) the proportion of time in each SpO_2 bin between ≤80% and 100%, with and without supplemental oxygen; (2) the mean proportion of time above and below normoxaemia; (3) the mean FiO_2 and SpO_2, as well as the median SpO_2 for the 2 min after oximeter drop-outs; (4) the number of FiO_2 adjustments and (5) the frequency and duration of episodes outside target range. Episodes were defined as consecutive 4 s data points. Prolonged episodes were defined as those lasting for at least 60 s. Two post hoc analyses were conducted. The time with SpO_2 between 90% and 95% during supplemental oxygenation was calculated, to assess the impact of differences in time on room air between automated and manual control. In addition,

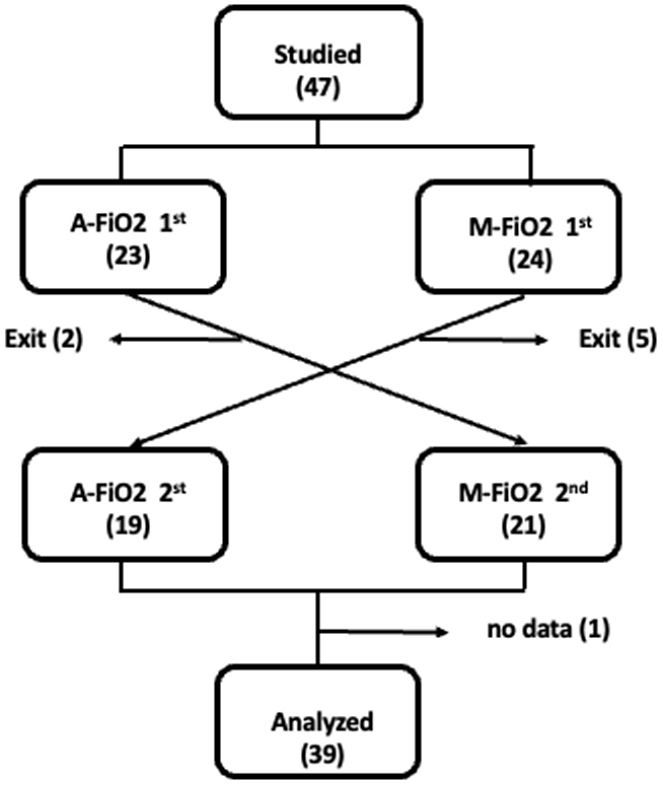

Figure 1 Subject accounting. The two patients exited in the first A-FiO_2 arm were at 22 and 24 hours (one was an intubation and the other an operator error (data logging turned off during manual intervention)). The five patients' exits from the first arm of M-FiO_2 were at 8, 19, 21, 24, 24 hours (two were weaned from HFNC, one was intubated and two were withdrawn by the attending). There were no early exits in the second arm during A-FiO_2. Four patients exited early in the second arm of M-FiO_2 at 5, 12, 14, 15 hours (two were an operator error with collection of SpO_2 data, one withdrawal by attending and one was extubated). FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula.

Table 1 Baseline enrolment

Subjects	39
Gender (% female)	18/39 (54)
Gestational age (weeks^{days})	27^4 (26^3–30^0)
Birth weight (grams)	980 (800–1335)
Age at entry (days)	7 (2–17)
Weight at entry (grams)	1120 (915–1588)
Indication for respiratory support	
RDS	20 (51%)
Respiratory Insufficiency	8 (21%)
BPD	6 (15%)
Other	5 (13%)
Surfactant (%)	33 (85%)
Caffeine (%)	25 (64%)
Antibiotics (%)	36 (63%)
Vasoactive drug (%)	6 (15%)
Invasive ventilation	12 (31%)
SIPPV/SIMV/HFO	7/4/1
Non-invasive support	27 (69%)
DuoPAP/CPAP/HFNC/NIPPV	12/10/4/1
Initial FiO_2 (%)	32 (22–43)
Previous use A-FiO_2 (%)	8 (21%)
First arm A-FiO_2 (%)	21 (54%)

Continuous parameters are presented as median (IQR) RDS, BPD, SIPPV, SIMV, HFO, DuoPA, CPAP, HFNC, NIPPV.
BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; DuoPAP, two level positive airway pressure; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HFO, high-frequency oscillation; NIPPV, nasal intermittent positive pressure ventilation; RDS, respiratory distress syndrome; SIMV, synchronised intermittent mechanical ventilation; SIPPV, synchronised intermittent positive pressure ventilation.

the primary outcomes were cross-tabulated by invasive and non-invasive respiratory support. To account for possible transition effects data from the first 10 min and last 5 min of each arm were excluded. All calculations of the proportion of time used time with an SpO_2 signal as the denominator.

Endpoints were unchanged except for the post hoc analyses noted above.

Statistical considerations

A meta-analysis of 14 similar A-FiO_2 cross-over study cohorts reported that A-FiO_2 improved time within the SpO_2 target range by 12.9%.[9] We determined that we would be able to detect a 4% (±6% SD) difference between A-FiO_2 and M-FiO_2 with an alpha of 5% and a power >90% with 40 infants. Assuming 15% would not complete the study, an enrolment of 47 patients was specified.

Based on intention to treat, all subjects with exposure to both interventions of any duration were included in the analyses. The three outcome endpoints were also calculated for all enrolled subjects, as a sensitivity analysis to determine if their exclusion affected the results.

Variables and differences between paired variables were tested for normality (Shapiro-Wilk test), which showed that nearly all were not normally distributed. Therefore, non-parametric tests were used to evaluate the difference between automated and manual control periods (Wilcoxon signed-rank or Mann-Whitney for paired and nonpaired data, respectively). To facilitate comparison to previous and inclusion in future meta-analyses, times in, above and below the target range are reported as mean and SD. For consistency of presentation, other parameters are reported as median and IQR. A two-tailed $p<0.05$ was considered statistically significant for all comparisons. 95% CI in the difference in mean was determined for the primary outcome. Statistical tests were conducted with XLSTAT V.11.5 (Lumivero, New York, USA).

Table 2 End points

	A-FiO2	M-FiO2	P value
n	39	39	na
Primary			
% time 90%–95% or above without O_2	74±22	51±22	<0.001
% time SpO_2<80%	0 (0–1)	0 (0–1)	ns
% time SpO_2>98% with suppl O_2	1 (0–3.5)	5 (1–10)	<0.001
Secondary			
% Time 90%–95% with FiO_2>0.21*	63±20	40±21	<0.001
% Time>95% with FiO_2>0.21*	16±19	35±24	<0.001
% Time SpO_2<90%	9±8	12±11	<0.001
Episodes<80% ≥4 s per day	9.0 (4.6–39)	16 (8.5–40)	0.041
Episodes<80% ≥60 s per day	1.0 (0.0–2.5)	1.0 (0.0–5.4)	ns
Episodes>98% with FiO_2>0.21 per day	41 (15–123)	142 (44–253)	0.002
Episodes>98% ≥60 s with FiO_2>0.21 per day	2.2 (0.0–9.0)	13.0 (3.9–29)	0.003

The values are presented as mean±SD or median (IQR).
*Calculated as %time with time in supplemental oxygen as the denominator.
FiO2, fraction of inspired oxygen; n/a, not applicable; ns, not significant.

RESULTS

Patients were enrolled between January and October 2022. Centres enrolled between 6 and 12 infants, accounting for a total of 47 infants. Eight subjects were excluded from the analysis: seven were not exposed to both control methods, and in one, no data were captured due to a technical problem (figure 1). Thus, 39 subjects, exposed to both A-FiO_2 and M-FiO_2, were included in the final intention-to-treat analyses.

The characteristics of the study population are shown in table 1. Most of the subjects were less than 2 weeks at enrolment. More than half were less than 1000 g when enrolled, and a quarter between 2900 and 4160 g. A total of 27 infants (69%) were receiving noninvasive support (13 intermittent nasal positive pressure ventilation, 10 continuous nasal positive airway pressure, 4 high-flow nasal cannula (HFNC)) and the remaining 12 infants (31%) were supported by invasive mechanical ventilation. Eight infants (21%) were receiving A-FiO_2 before study entry.

The primary outcome, time within normoxaemia and time at SpO_2 extremes are detailed in table 2. During A-FiO_2 control, the time in normoxaemia was higher than during manual control (74%±22% vs 51%±22%, respectively; p<0.001, mean difference 23%, 95% CI 16% to 30%). A-FiO_2 was associated with a decrease in time with SpO_2>98% when receiving supplemental oxygen (1% (IQR 0%–3.5%) vs 5% (IQR 1%–10%), p<0.001.

Table 3 Overview of intervention

	A-FiO2	M-FiO2	P value
n	39	39	na
Duration of intervention (hour)	23.7 (23.7–23.9)	23.7 (23.6–23.9)	ns
Mean SpO_2 (%)	92.9 (92.4–94.6)	94.0 (92.2–95.4)	0.025
SpO_2 dropouts (per day)	11 (5–16)	10 (6–16)	ns
Median SpO_2 after drop-out (%)	92 (91–95)	90 (87–92)	ns
Mean FiO_2 (%)	26 (23–40)	26 (23–27)	ns
Time in FiO_2=0.21 (%)	17 (2–51)	3 (0–27)	0.019
FiO_2 flushes per day	4 (1–15)	1 (0–5)	0.025
Manual FiO_2 adj per day	8.0 (4.5–12)	30 (17–106)	<0.001
Auto FiO_2 adjustments per hour	80 (50–108)	n/a	n/a

The values are presented as median (IQR). SpO_2 after dropout reflects subsequent 2 min. The flush function permits the clinician to trigger an increase in FiO_2 for a short period of time and can be used to preoxygenate or respond to a marked hypoxaemia. The level of FiO_2 and duration of flush are both set by the operator.
FiO_2, fraction of inspired oxygen; n/a, not applicable; ns, not significant.

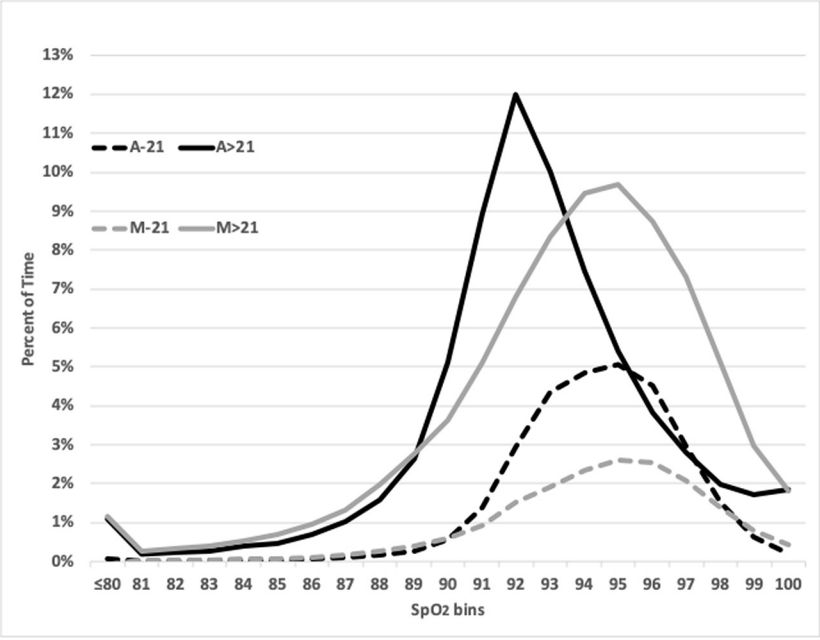

Figure 2 Histogram SpO_2 with and without supplement O_2. Histogram constructed with the mean of the subjects' SpO_2 in each bin. The grey lines are M-FiO_2 and the black A-FiO_2. The dashed lines are during periods without supplemental oxygen and the solid with supplemental oxygen. FiO_2, fraction of inspired oxygen.

Exposure to SpO_2<80% was low in both arms and not significantly different. The first post hoc analysis, which included all enrolled subjects (ie, those not exposed to both A-FiO_2 and M-FiO_2), was consistent with these findings. Finally, these results were similar for infants supported non-invasively or invasively (post hoc results in online supplemental materials).

Secondary descriptive endpoints were consistent with the primary outcome findings. As shown in table 2, there were fewer total episodes and fewer prolonged episodes of hyperoxaemia during A-FiO_2. In addition, there was no difference in number of prolonged episodes of hypoxaemia. There was, however, a slight reduction in the total number of severe hypoxaemic episodes associated with A-FiO_2.

Table 3 provides information on the course of the interventions. During A-FiO_2, automatic adjustments of FiO_2 were quite frequent (80/hour (IQR: 50–108), but manual adjustments were markedly lower than during M-FiO_2 (8.0/day (4.5–12) vs 30/day (17–106), p<0.001). The median FiO_2 and SpO_2 were similar in the two arms. However, during A-FiO_2 the infants spent more time on room air, with a slightly lower median SpO_2 (92.9% (92.4%–94.6%) vs 94.0% (92.2%–95.4%) p=0.025). The SpO_2 histogram in figure 2 shows the SpO_2 distribution during periods with and without supplemental oxygen. When receiving supplemental oxygen, there was a shift towards normoxaemia during A-FiO_2, which is more apparent than the small difference in SpO_2 medians (table 3). As expected during periods without supplemental oxygen, both histograms shifted to the right with similar and limited hypoxaemia exposure.

There were four adverse events reported during the study period, two in each treatment arm. A detailed description can be found in online supplemental material. In addition, four subjects spent more time in normoxaemia during manual control.

DISCUSSION

We conducted a multicentre pragmatic cross-over study to evaluate the performance of the PRICO A-FiO_2 system. We found that this A-FiO_2 system markedly increased time in normoxaemia which was mainly driven by a reduction in time spent in hyperoxaemia.

The difference in the mean time in the target range (23% (95% CI 16% to 30%)) is slightly higher than reported in two systematic reviews which included 14 studies investigating eight different A-FiO_2 systems.[9 10] The subgroup meta-analysis in one review, including only those studies using a target range of 90%–95% as we used, showed a difference of 18% (95% CI 5% to 32%).[9] Our finding is within these confidence limits. In addition to differences in the A-FiO_2 algorithms, the larger treatment effect might be related to manual oxygen titration practices, staffing levels and inclusion of bigger infants.

To date, three other studies have investigated the efficacy of the PRICO system in infants. These studies[12 13 17] reported a median improvement of the time within the target range between 6% and 16%, again considerably lower than this study. This larger difference between A-FiO_2 and M-FiO_2 seems to be mediated on the one hand by a higher percentage of time within the target range during A-FiO_2 with a lower percentage of time

within the target range in the M-FiO_2. While all studies, including ours, tended to reduce time above and below the target range, there was considerable variation in the reduction at SpO_2 extremes in the different studies. Two suggested a more prominent effect in reducing the time in severe hypoxaemia[13 17] while our study showed better performance of A-FiO_2 in avoiding severe hyperoxaemia. One study reported a decrease in severe hypoxaemia but did not report exposure to severe hyperoxaemia.[12] Although it is unclear what caused these differences in performance, it is important to emphasise, that there were important differences between the studies which may have impacted the efficacy of both automated and manual FiO_2 control. One study by Dijkman *et al*, only included infants on HFNC, which allows for a large leak at the nasal interface.[13] Two of the previous studies used a broader SpO_2 target range (88%–95%)[13 17] and a shorter measurement period (8 hours),[17] which may also have impacted performance. Finally, there were differences in the patient characteristics, such as gestational age, respiratory support modalities and the postnatal age at inclusion. Overall, these findings suggest that the relative effectiveness of an A-FiO_2 system is not fixed but will vary between different patients, target ranges and modes of respiratory support. As an example, two recent reports suggest the relative effectiveness of A-FiO_2 compared with M-FiO_2 is most marked in unstable infants.[17 18]

Although most of the focus when evaluating the performance of an A-FiO_2 system has been on the time in the intended SpO_2 target range, what happens with oxygenation during those episodes outside the target range is also of clinical importance. Especially, prolonged periods in extreme hyperoxaemia and hypoxaemia have been associated with neonatal morbidity in the short term and long term.[5 8] We found that the differences between A-FiO_2 and M-FiO_2 in per cent time at SpO_2 extremes were consistent with the number of prolonged episodes. This finding is consistent with other reports,[5 19] further supporting the premise that reducing prolonged episodes outside target range is associated with improved time in the target range and leads to potential long-term benefits of A-FiO_2.

Besides, the benefit of improved SpO_2 control, A-FiO_2 also promises to reduce nursing stress and labour. Only one of the previous studies of PRICO reported on the reduction in manual FiO_2 adjustments.[12] They reported a modest decrease of nine adjustments per day. In contrast we found a decrease of 22 per day (30–8). Clearly, the need for manual adjustments is dependent on the stability of the infant, which probably also explains the large IQR during manual control (upper quartile 106 adjustments/day) compared with automated control (upper quartile 12 adjustments/day).

We found no difference in the response to SpO_2 drop-outs between A-FiO_2 and M-FiO_2, suggesting PRICO's fall-back to a clinician's set FiO_2 level is as effective as nursing response. Others have suggested the importance of the response to drop-outs,[20] but we are unaware of published evaluations of the effectiveness of other A-FiO_2 fall-back strategies for periods without reliable SpO_2 readings.

Our report has some strengths and limitations. First of all, it enrolled more subjects than most evaluations of A-FiO2 systems. Also, the enrolment was not restricted to extremely preterm infants. In addition, it reflects a multicentre experience. While its cross-over design is the typical approach for evaluating the performance of an A-FiO_2 system, the differences identified in this type study might not be projectable to routine care. This was a pragmatic study which generally provides a better basis for projection to the impact in routine use, however, the impact of different approaches to respiratory care and settings are confounding. While another strength of the study was the use of A-FiO_2 in different respiratory support modes, the study was only powered to detect an overall difference in performance. Therefore, it was inadequate to evaluate the relative effect of different respiratory support modes. Particularly, additional studies during high-frequency oscillatory ventilation are warranted. Eight of the subjects were being managed by A-FiO_2 when randomised, but a previous study suggests that this probably does not affect our findings.[21] Finally, the study centres were all experienced with both the ventilator and the use of A-FiO_2, and the finding should be projected to naïve centres cautiously.

CONCLUSIONS

The study demonstrates the ability of the PRICO automated oxygen control algorithm to improve the maintenance of SpO_2 in normoxaemia and to avoid hyperoxaemia while reducing the need for nursing intervention, in a wide range of preterm infants supported with various respiratory support modalities.

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Contributors All the authors have critically reviewed and the manuscript. The manuscript was written by MW, TB, TS and AvK. MW, TS, BL, BRW and AvK supervised implementation of the study at their sites. In addition to those five, KWS, KC, KO, KJ, PP, WO, GJH and RWvL implemented the study at their site. TB is the guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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REFERENCES

1 Sweet DG, Carnielli VP, Greisen G, *et al*. European consensus guidelines on the management of respiratory distress syndrome: 2022 update. *Neonatology* 2023;120:3–23.
2 Hagadorn JI, Furey AM, Nghiem T-H, *et al*. Achieved versus intended pulse Oximeter saturation in infants born less than 28 weeks' gestation: the Aviox study. *Pediatrics* 2006;118:1574–82.
3 van Zanten HA, Tan RNGB, van den Hoogen A, *et al*. Compliance in oxygen saturation targeting in Preterm infants: a systematic review. *Eur J Pediatr* 2015;174:1561–72.
4 Askie LM, Darlow BA, Finer N, *et al*. Association between oxygen saturation targeting and death or disability in extremely Preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. *JAMA* 2018;319:2190–201.
5 Poets CF, Roberts RS, Schmidt B, *et al*. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely Preterm infants. *JAMA* 2015;314:595–603.
6 Raffay TM, Dylag AM, Sattar A, *et al*. Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age. *Pediatr Res* 2019;85:318–23.
7 Di Fiore JM, Bloom JN, Orge F, *et al*. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr* 2010;157:69–73.
8 Askie LM, Henderson-Smart DJ, Irwig L, *et al*. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med* 2003;349:959–67.
9 Abdo M, Hanbal A, Asla MM, *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.
10 Stafford IG, Lai NM, Tan K. Automated oxygen delivery for preterm infants with respiratory dysfunction. *Cochrane Database Syst Rev* 2023;11:CD013294.
11 Salverda HH, Cramer SJE, Witlox RSGM, *et al*. Automated oxygen control in preterm infants, how does it work and what to expect: a narrative review. *Arch Dis Child Fetal Neonatal Ed* 2021;106:215–21.
12 Dani C, Pratesi S, Luzzati M, *et al*. Cerebral and splanchnic oxygenation during automated control of inspired oxygen (Fio_2) in preterm infants. *Pediatr Pulmonol* 2021;56:2067–72.
13 Dijkman KP, Mohns T, Dieleman JP, *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 Ed* 2021;106:621–6.
14 Hütten MC, Goos TG, Ophelders D, *et al*. Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. *Pediatr Res* 2015;78:657–63.
15 Bachman TE, Iyer NP, Newth CJL, *et al*. Thresholds for oximetry alarms and target range in the NICU: an observational assessment based on likely oxygen tension and maturity. *BMC Pediatr* 2020;20:317.
16 Bachman TE, Newth CJL, Iyer NP, *et al*. Hypoxemic and hyperoxemic likelihood in pulse oximetry ranges: NICU observational study. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F274–9.
17 Dijkman KP, Goos TG, Dieleman JP, *et al*. Predictive intelligent control of oxygenation in preterm infants: a two-center feasibility study. *Neonatology* 2023;120:235–41.
18 Bachman T, Rafl J, LeMoyne R. Comparison of the relative effectiveness of automated Fio_2 control in neonates of differing stability: individual patient analysis. *EPNV Conf* 2023.
19 Bachman TE, Onland W, van Kaam AH, *et al*. Frequency and duration of extreme hypoxemic and hyperoxemic episodes during manual and automatic oxygen control in preterm infants: a retrospective cohort analysis from randomized studies. *BMC Pediatr* 2022;22:350.
20 Lim K, Wheeler KI, Jackson HD, *et al*. Lost without trace: oximetry signal dropout in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F436–8.
21 Bachman T, Roubik K. Crossover from automated to manual titration of Fio2 in the NICU: is there a transition lag? *Clin Technol* 2016;46:37–40.