Oxygen titration and compliance with targeting oxygen saturation in preterm infants

Zanten, H.A. van

Chapter 4

Improving manual oxygen titration in preterm infants by training and guideline implementation

Henriëtte A. van Zanten
Steffen C. Pauws
Evelien C. Beks
Ben J. Stenson
Enrico Lopriore
Arjan B. te Pas

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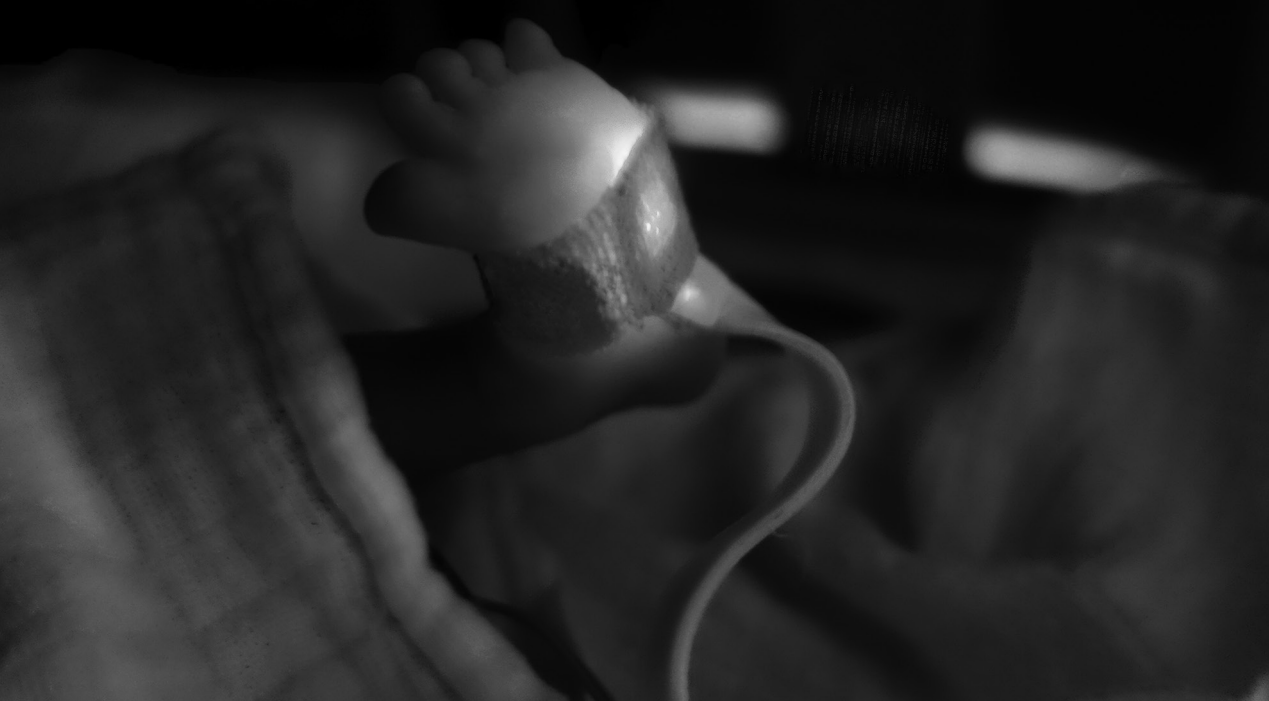

ABSTRACT

Two cohorts of preterm infants <30 weeks of gestation needing respiratory support and oxygen therapy were compared, to study oxygen saturation (SpO_2) targeting before and after training and guideline implementation of manual oxygen titration. The percentage of time spent with SpO_2 within target range (85-95%) was calculated (%SpO_2-wtr). SpO_2 was collected every minute when fraction of inspired oxygen (FiO_2) >0.21. ABCs where oxygen therapy was given were identified and analysed.

After training and guideline implementation the %SpO_2-wtr increased (median (IQR) 48.0(19.6-63.9)% vs 61.9(48.5–72.3)%;*p*<0.005), with a decrease in the %SpO_2 >95% (44.0(27.8–66.2)% vs 30.8(22.6–44.5)%;p< 0.05). There was no effect on the %SpO_2 <85% (5.9(2.8 – 7.9)% vs 6.2(2.5 - 8)%;ns) and %SpO_2 <80% (1.9(1.0 – 3.0)% vs 1.7(0.8 – 2.6)%; ns). In total 186 ABCs with oxygen therapy before and 168 ABCs after training and guideline implementation occurred. The duration of SpO_2 <80% reduced (2(1-2) vs 1(1-2) minutes;*p*<0.05), the occurrence of SpO_2 >95% did not decrease (73% vs 64%;ns), but lasted shorter (2(0-7) vs 1(1-3) minutes;*p*<0.004).

Conclusion: Training and guideline implementation in manual oxygen titration improved SpO_2 targeting in preterm infants with more time spent within target range and less frequent hyperoxaemia. The durations of hypoxaemia and hyperoxaemia during ABCs were shorter.

What is known

Targeting SpO_2 in preterm infants can be challenging and the compliance is low when oxygen is titrated manually.

Hyperoxaemia occurs often after oxygen therapy for oxygen desaturation during apnoeas.

What is new

Training and implementing guidelines improved targeting SpO_2 and reduced hyperoxaemia.

Training and implementing guidelines improved manual oxygen titration during apnoea, combined with bradycardia and cyanosis (ABC).

INTRODUCTION

Oxygen is the most commonly used therapy in neonatal intensive care units (NICUs).[6] To assure adequate delivery of oxygen to the tissue without creating oxygen toxicity, [64] infants admitted to the NICU are continuously monitored using pulse oximetry. Oxygen is titrated manually to maintain the pulse oxygen saturation (SpO_2) within target ranges (TR), but this can be challenging. Several studies reported low compliance in targeting SpO_2 and described a tendency of caregivers to accept higher SpO_2.[18 20 24 30 31 40 41] It has been suggested that caregivers are more focused to prevent hypoxaemia than hyperoxaemia.[10 32] However, improving the knowledge of caregivers in the hazards of hyperoxaemia could lead to more vigilance against alarm settings and oxygen titration and thus decrease the time outside TR in preterm infants considerably.[10]

Oxygen is most frequently manually titrated when an apnoea occurs, apnoea is defined as a respiratory pause >20 seconds and/or shorter accompanied by bradycardia or cyanosis, hypotonia and pallor (usually termed ABC: apnoea, bradycardia, cyanosis).[65] We recently demonstrated that manual titration of oxygen therapy in preterm infants during ABC unintendedly led to the occurrence of hyperoxaemia (SpO_2 >95%).[24] To improve compliance, especially during ABCs, all neonatal caregivers in our NICU received additional training about the risk of hypoxaemia and hyperoxaemia, and a guideline for manual oxygen titration was introduced.

Efforts have been taken to increase the nurses' compliance in SpO_2 targeting by creating awareness by training and implementing guidelines, with variable success.[29 37 48-50 66] We aimed to investigate the effect of training combined with an oxygen titration guideline on the proportion of time SpO_2 was within TR (%SpO_2-wtr) and the occurrence and duration of hypoxaemia and hyperoxaemia during and after ABCs.

METHODS

A prospective observational study was performed at the NICU of the Leiden University Medical Centre (LUMC), which is a tertiary level perinatal centre in the Netherlands with an average of 650 intensive care admissions per year. This study was an audit and part of a quality improvement project and did not need to comply with the Dutch law on Medical Research in Humans; the Research Ethics Committee issued a statement of no objection. All infants born <30 weeks of gestation admitted to the NICU in LUMC between March 2013 and December 2013 (before training and guideline implementation) and between

February 2014 and November 2014 (after training and guideline implementation) were retrospectively compared.

To increase awareness in SpO_2 targeting and oxygen titration, all caregivers were trained in a months' period (January 2014). Before the afternoon shift started, nurses were asked to attend a lesson that lasted 30-45 minutes. Each session was attended by 6-8 nurses. An attendance list was updated to make sure every nurse attended the lesson. The medical staff was trained separately during a grand round session. The training was given by the nurse (first author) or neonatal consultant (last author) responsible for the quality improvement project. During this training the results of our previous study were discussed, which demonstrated frequent occurrence of hyperoxaemia after ABCs when oxygen therapy was given.[24] Caregivers were also educated in the risks of exposure of preterm infants to frequent hypoxaemia and hyperoxaemia. To pursue an uniform approach to oxygen titration, a guideline for oxygen titration was introduced and discussed (Figure 1). After the training, the nurse and consultant responsible for the project were available during daytime and frequently actively approached the staff whether there were questions or issues related to the oxygen titration and/or the guideline. Also, the medical staff was asked to standardly check the SpO_2 distribution during the daily rounds.

The guideline was specially developed for a randomised trial comparing manual versus automated oxygen titration.[67] During the trial the nurses used the guideline during the manual periods. The guideline was then discussed by members of the project and the nurses that received special training in ventilation. Based on their feedback, small amendments were made to make it more practicable for the nurses.

All preterm infants receiving respiratory support (endotracheal and non-invasive ventilation) in the NICU were included in the study. Infants with major congenital heart disease with different SpO_2 target ranges were excluded. All infants received routinely a loading dose of 10 mg/kg caffeine base directly after birth followed by 5 mg/kg/day. Dopram (2 mg/kg/hr) was given in case of refractory apnoeas. Respiratory support was given by a mechanical ventilator (AVEA, Carefusion, Houten, The Netherlands), which was connected to the patient data management system (PDMS) (Metavision; IMDsoft, Tel Aviv, Israel). SpO_2 was measured using Masimo SET Radical pulse oximeter (software version 46.02) (Masimo Radical, Masimo Corporation, Irvine CA, USA), integrated in the bedside monitor (Philips Healthcare Nederland, Eindhoven, The Netherlands). The pulse oximeter probe was placed around the hand or foot of the infant. (right hand in case of a patent ductus arteriosus). Basic characteristics were collected from the patient files in PDMS. All clinical parameters were collected every minute from PDMS. In both periods, the SpO_2 TR was 85-95% when

FiO_2 >0.21 and the alarm limits were set at 84% and 96%.Before the start of each shift, the TR and alarm setting were checked by the nurse.
%SpO_2-wtr, SpO_2 < 85% and SpO_2 > 95%, when FiO_2 >0.21 was calculated for each patient during the time period infants received respiratory supported. Additionally, all ABC events were documented and evaluated in all preterm infants on non-invasive ventilation (nasal CPAP and non-invasive intermittent mandatory ventilation). An ABC was defined as apnoea (>20 seconds or shorter), accompanied with bradycardia (<80 beats per minutes (bpm)) and cyanosis (SpO_2 <80%). As data is sampled every minute, every ABC where supplemental oxygen was titrated was evaluated by documenting the following characteristics: lowest stored minute value (depth) and count in low minute values (duration) of HR <80 bpm, lowest stored minute value (depth) and the count in low minute values (duration) of SpO_2 <80%, baseline oxygen concentration and additional oxygen supplied, the count in minute values with additional oxygen, occurrence and count in minute values with SpO_2 >95%. Hypoxaemia was defined as SpO_2 <80% and hyperoxaemia as SpO_2 >95%.
All ABCs were manually identified in PDMS and analysed starting at the occurrence of an ABC and was continued until the supplemental oxygen administered was returned to the baseline oxygen level before the ABC occurred.

Statistical analyses
Quantitative data are presented as median (IQR), mean (SD) or number (percentage) where appropriate. Time with SpO_2 within various ranges for FiO_2 >0.21 were collated for each infant individually before and after training and aggregated as proportions of the recorded time (median and IQR). Statistical analysis comprised non-parametric Kruskal-Wallis rank sum test. The Mann Whitney U test was used for non-parametric comparisons for continuous variables to compare the patient characteristics and the ABC characteristics. P-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Software, NY, USA, 2012) and R 3.2.0 (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

We considered an increase of 10% SpO_2-wtr clinically relevant. In previous studies the standard deviation of the mean %SpO_2-wtr was 16.[67] To detect a change of 10% SpO_2-wtr in each period by a Kruskal-Wallis test with a 80% power and a significance level of 0.05 (two-tailed test), at least 44 patients in each group were required. This number was calculated by running a simulation taking samples from two normal distributions with means 0 and 10 and a standard deviation of 16 to model the clinically relevant increase in %SpO2-wtr.

RESULTS

Patient characteristics

During the two study periods of 10 months, a total number of 136 infants born <30 weeks of gestation were admitted to our NICU. Of these infants, 79 infants were admitted and treated before education on oxygen titration and the implementation of a guideline, 57 infants after were admitted after these changes. The median interquartile range (IQR) of gestational age was (28+2 (27+3 - 29) vs 28+3 (26+4 -29) weeks; ns) and birth weight (1090 (857-1277) vs 1000 (855-1206); ns) were not different (Table 1).

Table 1. Patient characteristics

	Before Training N= 79	After Training N= 57	*p*-value
Gestational age at birth (weeks), Median (IQR)	28+2 (27+3 - 29)	28+3 (26 +4 – 29)	0.36 [a]
Birth weight (grams) median (IQR)	1090 (857-1277)	1000 (855 – 1206)	0.56 [a]
Male sex, no (%)	46 (58)	32 (56)	0.96 [b]
Caesarean delivery, no (%)	39 (49)	31 (54)	0.56 [b]
Singletons, no (%)	51 (65)	39 (68)	0.26 [b]
Apgar at 5 min. median, (IQR)	7 (7-8)	7 (6-9)	0.66 [a]
Days on respiratory support, median (IQR)	9 (3-14)	8 (4-24)	0.89 [a]
Length of stay on NICU, median (IQR)	15 (8-25)	19 (8-35)	0.32 [a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

Effect of training and guideline on the %SpO_2-wtr

There was a small but significant decrease in median SpO_2, where IQR remained similar (before vs after training: 94% (91-96)% vs 93% (91-96)%;*p*=0.02). After training and guideline implementation the %SpO_2-wtr significantly increased (before vs after training: 48.0 (19.6 - 63.9)% vs 61.9 (48.5 – 72.3)%; p <0.005), with a simultaneous decrease in SpO_2 >95% (44.0 (27.8 – 66.2)% vs 30.8 (22.6 – 44.5)%; p <0.05) and a non-significant decrease in SpO_2 >98% (9.4 (4.2 – 26.8)% vs 6.1 (2.3 - 12.1)%; ns). %SpO_2 <85% remained similar (5.9 (2.8 - 7.9)% vs 6.2 (2.5 – 8.0)%; ns) as well as SpO_2 <80% (1.9 (1.0 – 3.0)% vs 1.7 (0.8 – 2.6)%; ns) (Table 2, Figure 2).

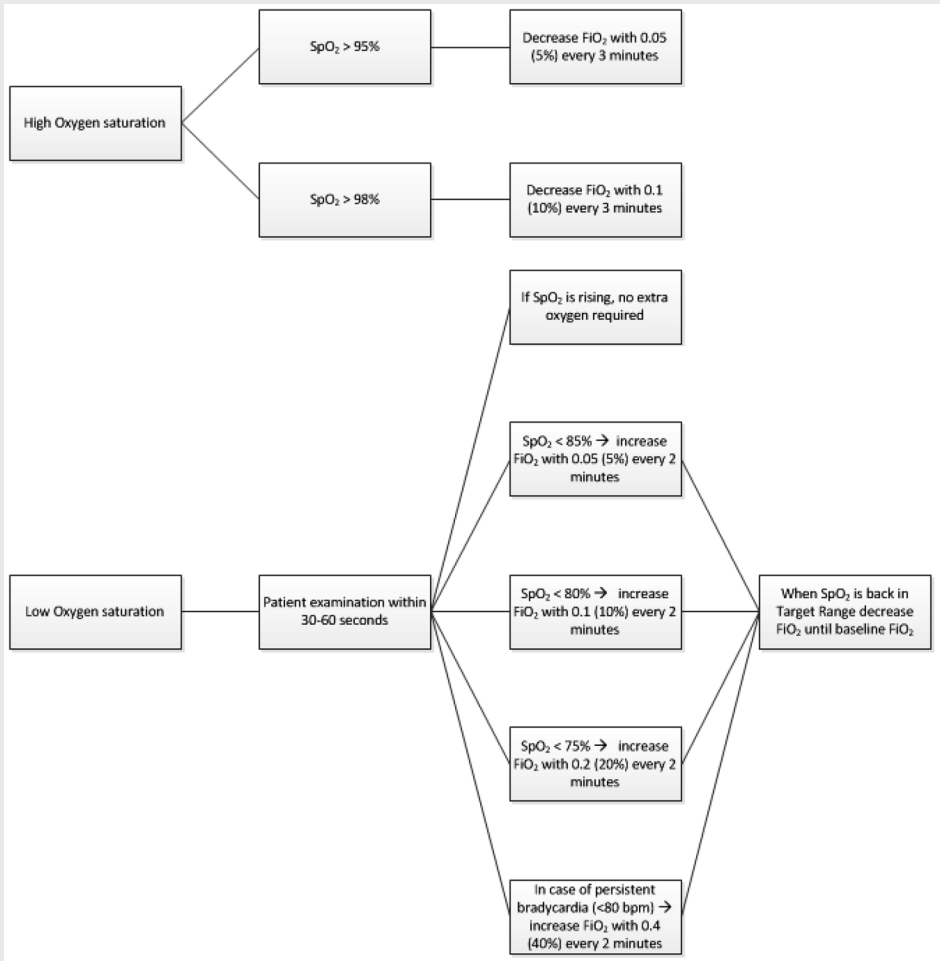

Figure 1. FiO_2 titration guideline

Table 2. Median (IQR) in different saturation ranges

	Before Training	After Training	*p*-value*
%SpO_2 <80%	1.9 (1.0 - 3.0)	1.7 (0.8 - 2.6)	ns
%SpO_2 <85%	5.9 (2.8 - 7.9)	6.2 (2.5 - 8.0)	ns
%SpO_2 - WTR 85-95%	48.0 (19.6 - 63.9)	61.9 (48.5 - 72.3)	< 0.005
%SpO_2 >95%	44.0 (27.8 - 66.2)	30.8 (22.6 - 44.5)	< 0.05
%SpO_2 >98%	9.4 (4.2 - 26.8)	6.1 (2.3 to 12.1)	< 0.06

* Statistical analysis comprised nonparametric Kruskal-Wallis rank sum test.

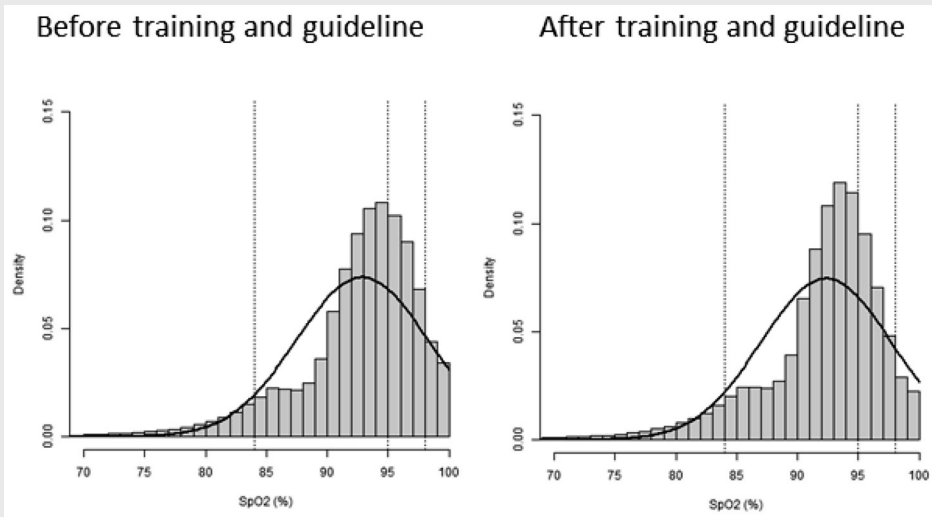

Figure 2. Time with SpO_2 within various ranges collated over all infants and aggregated as total proportion of recorded time

Effect of training and guideline on the occurrence of ABCs

Before training and guideline implementation, 79 infants received non-invasive respiratory support, of which 29/79 (37%) infants had a total of 186 ABCs that required extra FiO_2. After training and guideline implementation, 57 infants received non-invasive respiratory support and 28/57 (49%) infants had a total of 168 ABCs (Table 3). After training and guideline implementation the depth and duration of bradycardia did not change. Although no difference was observed in the depth of SpO_2 <80% during an ABC, the duration of SpO_2 <80% decreased significantly (2 (1-2) minutes vs 1 (1-2) minutes;*p* <0.05) (Table 4). Although the baseline and the maximum increase in FiO_2 during the ABC did not change, the duration of titrating oxygen back to the baseline concentration had a smaller range (3 (2-16) minutes to 3 (2-7) minutes;*p*< 0.05). There was no significant change in the occurrence of hyperoxaemia

after ABCs (73% (135/186) vs 64% (108/168); ns), but the duration significantly decreased from 2 (0-7) minutes to 1(1-3) minutes;p<0.01) (Table 4).

Table 3. Patient characteristics with ABCs.

	Before Training N= 29	After Training N= 28	*p*-value
Gestational age at birth (weeks), Median (IQR)	27+6 (26+5 - 29)	27+2 (26 – 28 +2)	0.19[a]
Birthweight (grams). Median (IQR)	1016 (812-1199)	965 (692 – 1199)	0.51 [a]
Male sex, no (%)	22 (76)	16 (57)	0.14[b]
Caesarean delivery, no (%)	13 (45)	15 (53)	0.51[b]
Singletons, no (%)	22 (76)	22 (79)	0.57 [b]
Apgar at 5 min, Median (IQR)	8 (7-8)	7 (6-9)	0.25[a]
Days with respiratory support, no. Median (IQR)	14 (8-32)	19 (9 -31)	0.5 [a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

Table 4. ABC characteristics with FiO_2-therapy

	Before Training (ABC= 186)	After Training (ABC = 168)	*p*-value
ABC with SpO_2 > 95%	73%	64%	ns[b]
Number of ABC, n. Median (IQR)	4 (1-9)	4 (2-8)	0.64[a]
Lowest minute value during bradycardia, bpm (dept) Median (IQR)	70 (60-75)	69 (61-75)	ns[a]
Count minute values with bradycardia, min (duration) Median (IQR)	1 (1-1)	1 (1-1)	ns[a]
Lowest minute value during SpO_2 <80%, % (dept)	70 (62-76)	72 (61-77)	ns[a]
Count minute values SpO_2 <80%, min (duration) Median (IQR)	2 (1-2)	1 (1-2)	0.03[a]
Baseline FiO_2	0.25 (0.21-0.31)	0.25 (0.21-0.30)	ns[a]
Max increase FiO_2	0.44 (0.39-0.52)	0.43 (0.37-0.51)	ns[a]
Count minute values of FiO_2 titration to baseline oxygen concentration, min Median (IQR)	3 (2-16)	3 (2-7)	0.010[a]
count minute value with SpO_2 >95%, min Median (IQR)	2 (0-7)	1 (1-3)	0.004[a]

[a] Independent samples Mann-Whitney U test
[b] Chi-square test

DISCUSSION

In this study extra training and implementation of a guideline for oxygen titration showed to improve the compliance of caregivers in our NICU in oxygen targeting and a more prompt handling of ABCs. Preterm infants receiving oxygen spent significantly more time within the SpO_2 TR of 85-95%, with a significant decrease in time of SpO_2 levels above 95%. The occurrence of hypoxaemia and hyperoxaemia during ABCs did not decrease, but both episodes lasted significantly shorter. This initiative in quality improvement had a positive effect and if the observed reduction in the risk for hypoxaemia and hyperoxaemia could be maintained through repetitive training, it would be likely to improve the outcome of preterm infants.

Previous studies have reported a quality improvement in oxygen titration and targeting SpO_2, using an approach comparable to ours.[48 50 68] The problems were initially assessed, followed by embedding education and implementation of a protocol, after which effectiveness was evaluated. In line with our findings, Ford *et al*. reported a significant improvement in time spent within the TR (90%-95%) and a reduction of SpO_2 above TR.[50] Lau *et al*. did not report the time spent within TR (85%-92%), but observed a significant reduction in SpO_2 ≥93%.[48] Also, in the study of Chow *et al.* the time spent within TR was not reported. They observed a decrease in severe retinopathy of prematurity (ROP) after introduction of an educational program combined with a titration protocol.[48 50 68] As the findings were similar in most performed studies, including ours, it is plausible that this approach (training and guideline implementation) can be successful in nearly all neonatal units.

It is unclear which part of the quality improvement has contributed most to the effect on the compliance of caregivers in oxygen titration and targeting SpO_2. Previous studies reporting the effect of guideline or education only were less successful compared to our study.[37 69 70] Clarke *et al*. reported no improved time within TR using an a titration guideline. Arawiran *et al.* observed no improved adherence to TR (85 - 92%) after an education intervention with oral and online presentations, discussions of adverse effects of excessive oxygen, and displaying SpO_2 distributions.[37] Also, Deuber *et al*. studied the effect of training with the aim to reduce hyperoxaemia and to increase caregivers knowledge. The time spent within TR (88% - 92%) was not reported, the time above TR was increased after training.[49] However, there are many variables that could have influenced the effect of training. Differences in content, approach and duration of the training, but also the general workload and nurse:patient ratio could have influenced the results.[40] As part of our education we discussed the results of our previous study, showing that SpO_2 >95% occurred in 79% of the ABCs where oxygen was increased.[24] During the training we observed that caregivers felt personally addressed, resulting in behavioral change by better titration of oxygen during apnoeas.

It is clear that guidelines were not followed exactly, and compliance with the exact timing and step size was not measured. Nevertheless, when presented as part of the training the guidelines provided a realistic framework on how to avoid hyperoxaemia, without increasing hypoxaemia. When the guideline was introduced and implemented in our unit we took into account the factors that are important for adopting a guideline. Factors related to organization (i.e. support from physicians), to nurses (i.e. awareness of, and attitudes towards guidelines), anticipated consequences (i.e. benefit to the patient and to nurses' work) and factors related to the patient group (i.e. topic of the guideline) were identified as important factors for adopting a guideline.[71] To get all caregivers involved, the guideline was openly discussed during the training sessions.

Recently, we reported on how nurses responded to an ABC and handled the oxygen titration.[24] In a retrospective study in preterm infants on nCPAP, we observed that when supplemental oxygen was given to treat ABCs, iatrogenic hyperoxaemia occurred and lasted significantly longer than the bradycardia or hypoxaemia that initially prompted the supplemental oxygen administration. Although the duration of hypoxaemia was comparable, the duration of hyperoxaemia was significantly longer (14 (4-52) minutes) in our previous study compared to our current observations in the cohort before the intervention. A possible explanation could be the use of the "increase FiO_2" key on the AVEA-ventilator. When this key is activated, the ventilator increases the oxygen concentration delivered to the infant for two minutes, after which the ventilator will return to prior settings. Nevertheless, training and guideline implementation significantly reduced the duration of hypoxaemia and hyperoxaemia even further. Apparently nurses were more prompt in their handling when an ABC occurred, but also titrated more carefully. Poets *et al*. found an increased risk of adverse outcomes in preterm infants who experienced intermittent hypoxaemia, lasting for approximately one minute or more.[14] This emphasizes the need for awareness and accurate handling of ABCs by the nurses.

In recent years, there is an increasing interest in automatic titration of oxygen in preterm infants. Closed-loop devices designed for monitoring and controlling the oxygenation in (ventilated) preterm infants are clinically used in research related context.[35 36 38 39] These studies have shown that using automated oxygen control significantly increased time of $\%SpO_2$-wtr of approximately 8-24%, however, the time outside TR varied between studies. Most studies, but not all, reduced hyperoxaemia, and some also reduced hypoxaemia.[35 36 38 39] Our study within manual control showed comparable results with automatic devices concerning the increased time $\%SpO_2$-wtr and decreased time $\%SpO_2$ above TR. To make sure that this effect remains, repetitive training should be implemented in our unit.

Recent randomised controlled trials demonstrated a lower mortality in preterm infants when SpO_2 was targeted 91-95% as compared to 85-89%.[15 43 44 72 73] In the time period of this observational study, our local guidelines recommended 85-95%, but were changed to 90-95% after the study. It is possible that this change could lead to different results when measuring the effect of training and guideline implementation. Jones et al. recently demonstrated that preterm infants with bronchopulmonary dysplasia (BPD) were much more stable and less difficult to target when higher SpO_2 targets were used.[74]

A limitation of this study is its retrospective character. The training and oxygen titration guidelines were initiated for quality improvement in our unit and for this reason the effect was audited by comparing the situation before and after the interventions instead of a randomised trial. The dip in the frequencies of SpO_2 87-90% is associated with the generation of Masimo oximeters available in our unit at the time of this study, using an internal calibration algorithm that reduces the frequency of saturations of 87–90% and increases the frequency of higher values.[75] However, this would not have influenced the effect of training and guideline implementation as both groups were measured with the same oximeters.

Furthermore, we did not adjust for the contribution of the amount of ABCs of each patient, but we considered every ABC as an independent event as all ABCs are handled the same for each infant. An important factor that could have influenced the results is the workload of caregivers. However, the nurse:patient ratio, the number of patients, severity of illness and NICU admissions days were not different between the periods, which makes it unlikely that the workload differed between periods. In addition, based on findings in recent large trials in SpO_2, in our unit the TR was narrowed towards the higher end (90-95%). It is possible that different results will be reached as it will be more difficult to comply with a smaller TR.

CONCLUSION

Based on the observations of this study, training of caregivers combined with an oxygen titration guideline, improved the compliance to stay within SpO_2 TR in preterm infants. Additionally the amount of hyperoxaemia reduced, without an increase of hypoxaemia. Thereby, oxygen was better titrated and reduced the duration of hyperoxaemia after ABCs.