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Oxygen titration and compliance with targeting oxygen saturation in preterm infants

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Citation

Zanten, H. A. van. (2017, March 15). *Oxygen titration and compliance with targeting oxygen saturation in preterm infants*. Retrieved from https://hdl.handle.net/1887/46692

Version:	Not Applicable (or Unknown)
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Note: To cite this publication please use the final published version (if applicable).

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Author: Zanten, Henriëtte van
Title: Oxygen titration and compliance with targeting oxygen saturation in preterm infants
Issue Date: 2017-03-15

Chapter 2

Compliance in targeting oxygen saturation in preterm infants: a systematic review

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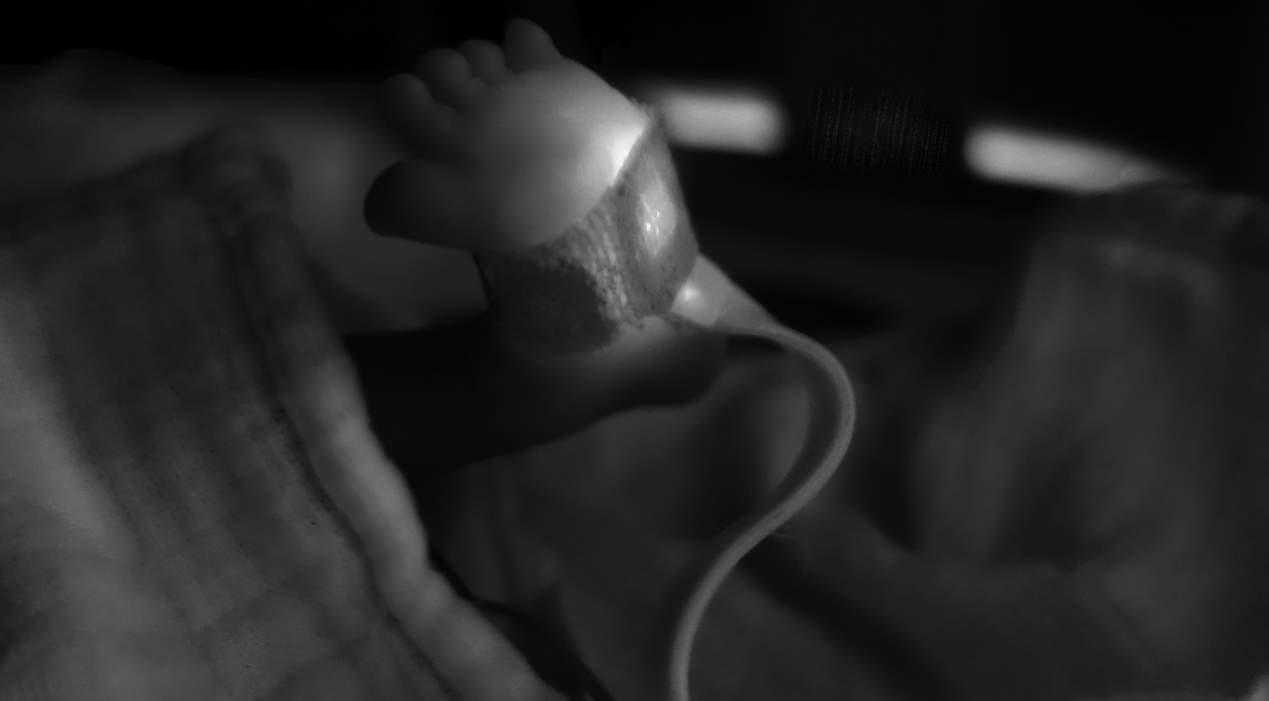
Eur J Pediatr. 2015 Dec;174(12):1561-72



ABSTRACT

During oxygen therapy in preterm infants, targeting oxygen saturation (SpO_2) is important to avoid hypoxaemia and hyperoxaemia but this can be very difficult and challenging to neonatal intensive care unit (NICU) nurses.

We systematically reviewed the qualitative and quantitative studies investigating the compliance in targeting SpO_2 in preterm infants and factors that influence this compliance. We searched PubMed, Embase, Web-of-Science, Cochrane, CINAHL, and ScienceDirect from 2000 to 2015. Sixteen studies were selected, which involved a total of 2935 nurses and 574 infants. The studies varied in methodology, and we have therefore used a narrative account to describe the data. The main finding is that there is a low compliance in targeting SpO_2; the upper alarm limits are inappropriately set, and maintaining the SpO_2 below the upper limit presented particular difficulties. Although there are little data available, the studies indicate that training, titration protocols and decreasing workload could improve awareness and compliance. Automated oxygen regulations have shown to increase the time SpO_2 is within the target range (TR).

Conclusion: The compliance in targeting SpO_2 during oxygen therapy in preterm infants is low, especially in maintaining the SpO_2 below the upper limit.

What is Known

The use of oxygen in preterm infants is vital, but the optimal strategy remains controversial. Targeting SpO_2 during oxygen therapy in preterm infants has shown to reduce mortality and morbidity.

What is New

Review of the literature showed that the compliance in targeting SpO_2 and alarm settings is low.

Creating awareness of risks of oxygen therapy and benefits in targeting, decreasing nurse:patient ratio, and automated oxygen therapy could increase compliance.

INTRODUCTION

Additional oxygen is often administered to preterm infants for hypoxemic episodes during respiratory distress or apnoeas. It is important to prevent hypoxaemia (defined as a decrease in blood saturation of ≤80% for ≥10 seconds) as frequent episodes could lead to an increased risk of morbidities, including retinopathy of prematurity (ROP), impaired growth, longer term cardio respiratory instability, and adverse neurodevelopmental outcome. In extreme cases it can even lead to death.[8 12] Hyperoxaemia (blood saturation of >95% for ≥10 seconds) also needs to be prevented as administering supplemental oxygen can potentially lead to high oxygen levels. High concentration of oxygen is toxic to living cells and is known to be an important pathogenic factor for bronchopulmonary dysplasia (BPD) and ROP [15], and is correlated with cerebral palsy.[9]

Pulse oximetry (PO) is most commonly used for continuous monitoring of oxygen saturation (SpO_2) in a non-invasive manner.[16] To prevent hypoxaemia and hyperoxaemia nurses usually titrate oxygen manually to maintain SpO_2 between the prescribed TR. However, maintaining the SpO_2 within this range can be challenging, and compliance – defined as the nurse's behaviour that follows the clinical guidelines[17] is influenced by several factors.[24] This compliance is important as it can largely influence the effect of a certain SpO_2 target range (TR). The optimal range of SpO_2 for preterm infants remains undefined, but recent trials have shown that aiming for 91-95% decreased mortality but increased incidence of ROP.[25] However, oxygen was titrated manually in these trials, which caused a large overlap in the distribution of SpO_2 between the two groups and may have decreased the observed differences in outcome.

Although comparison of SpO_2 TR has been subject to systemic review,[26] a review in the compliance in oxygen targeting is not available but equally important as the optimal TR. The purpose of this study is to systematically review the available literature in compliance - and the factors influencing this compliance - in targeting SpO_2 in preterm infants.

METHODS

We performed a systematic review, following PRISMA guidelines where possible (Figure 1).[27] The aim of the PRISMA statement is to help authors improve the reporting of systematic reviews and meta-analyses, which made it a particularly useful framework for this report. Eligible studies were identified by searching online databases from January 2000 to January 2015 in PubMed, Embase, Web-of-Science, Cochrane, CINAHL, and ScienceDirect (keywords in Table 1). After selecting the eligible studies, we manually searched the reference lists of the selected studies to identify additional references. The criteria for inclusion limited

the selection to articles published in English or Dutch which referred to preterm infants, (nursing) compliance, SpO_2 monitoring by PO, and targeting SpO_2 during admission at the neonatal intensive care unit (NICU). Both qualitative and quantitative designs were included, but publications that were not primarily research studies, i.e. letters, abstracts, reviews and editorials, were not (Figure 1). Three authors (HvZ, RT, AH) independently graded the selected studies using the QualSyst tool for quantitative and qualitative studies.[28] In case of disagreement, consensus was reached through discussion or consultation of a fourth co-author (AtP). The QualSyst tool for quantitative studies is a validated generic checklist consisting of fourteen items with scores from zero to two and the possibility to score 'not applicable'. Items rated 'not applicable' were excluded from the calculation of the summary score. The maximum total score is 28. The summary score was calculated by summing the total score obtained across the relevant items and dividing that by the total possible score.

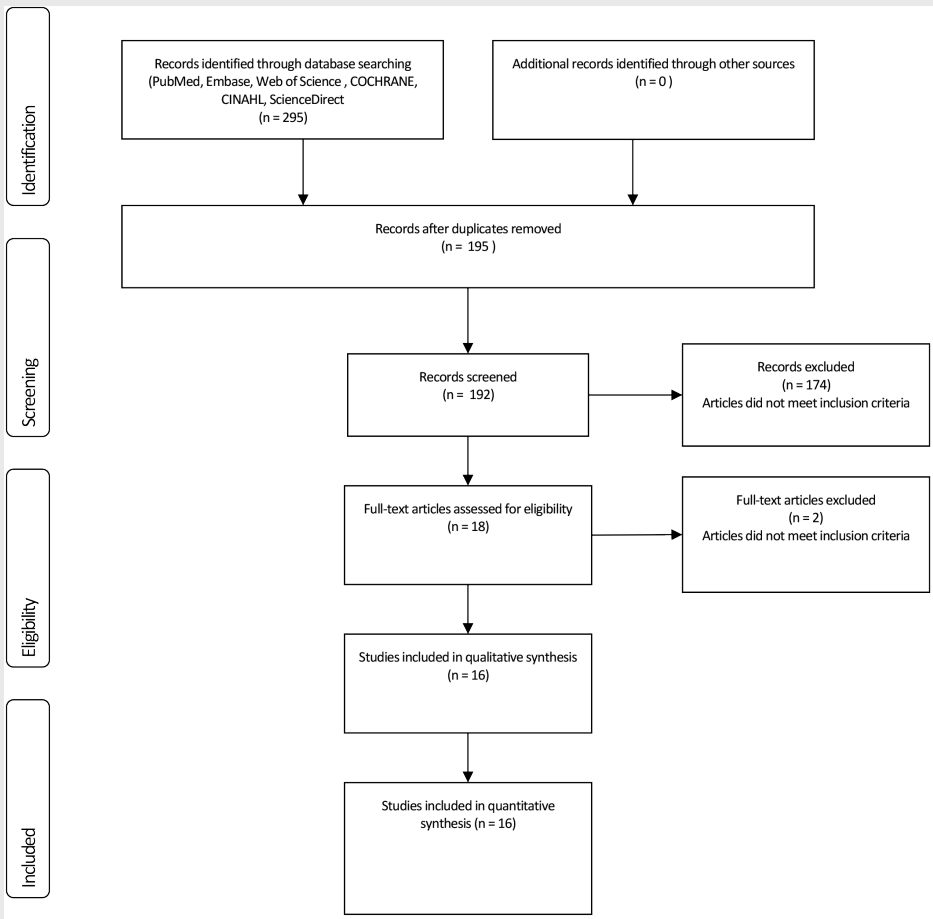


Figure 1. Flow diagram selected studies

Table 1. Keywords in different databases

Database	Keywords (including MeSH) terms
PubMed	Hyperoxia+, Hyperoxia*, hyperoxygenation, Hyperoxias, Hyperoxie, Hyperoxic, Hyperox*, hyperoxemic episode, hyperoxemic episodes,hypoxia, hypox*, hypoxemic episode, hypoxemic episodes, cyanosis cyanoses pulse oximetry, pulse oximeter, pulse oximeters, *Infant+, Premature+, prematurity, prematur*, Pre-mature, pre-maturity, preterm, preterm*, low birth weight infant, low birth weight infants,* **Oxygen Inhalation Therapy+, Hyperbaric Oxygenation+, Oxygen/administration and dosage+,oxygen/therapeutic use+ Oxygen/therapy+, Oxygen/Consumption+, oxygen consumption, oxygen, oxygenation, FiO2, FiO 2, FiO(2),FiO, increas*, fraction* exposure*, increase oxygen, increased oxygen, oxygen supplementation, oxygen therapy, supplemental oxygen,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, Oxygen Inhalation Therapy/ instrumentation+, Respiration, Artificial/instrumentation+ ***complia*, nursing compliance, Adherence, adher*, Guideline Adherence+, Advance Directive Adherence+, Goals+, nursing procedures***
CINAHL	Hyperoxia, hyperoxias, Hyperoxia* hyperoxygenation, hyperoxie, hyperoxic, hyperox* cyanosis, cyanoses, hypoxia*,pulse oximetry, pulse oximeter, pulse oximeters, *prematur*, Prematurity, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant,low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure***, *exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration,oxygen therapy,* *Automated closed loop control,FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control,* ***compliance, complia*, nursing compliance, Adherence, adher****
Web of Science	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, cyanosis, cyanoses pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, hypoxemic episodes, hyperoxemic episodes, hypoxemic episode, hyperoxemic episode, cyanosis, cyanoses, *premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, elbw infant*, low birth weight infant*,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure, exposures, exposure*,increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, compliance, complia*, nursing compliance, Adherence OR adher*
Embase	Hyperoxia/, pulse oximetry/, exp Hypoxia/, Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, pulse oximetry, pulse oximeter, pulse oximeters, hypoxia, hypoxemic episodes, hyperoxemic episodes" hypoxemic episode, hyperoxemic episode, cyanosis/, cyanosis, cyanoses, *prematurity/, premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2,FiO(2),FiO) increas*, fraction,fractions, fraction*, exposure, exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy, exp oxygen therapy/,oxygen saturation/,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control,oxygen delivery device/, exp* ***patient compliance/ compliance, complia*, nursing compliance, Adherence, adher* "nursing procedures"***
Sciencedirect	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*,pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, cyanosis, cyanoses*, premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO,increas*, fraction, fractions, fraction*, exposure, exposures, exposure*, increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, ***compliance OR complia* OR nursing compliance OR Adherence OR adher****
Cochrane	Hyperoxia, Hyperoxias, Hyperoxia*, Hyperoxie, Hyperoxic, hyperoxygenation, Hyperox*, pulse oximetry, pulse oximeter, pulse oximeters, hypoxia*, *premature, Prematurity, prematur*, pre-mature, pre-maturity, preterm, preterm*, pre-term, low birth weight infant, low birth weight infants,* **Oxygen*, FiO2, FiO 2, FiO(2), FiO, increas*, fraction, fractions, fraction*, exposure, exposures, exposure*,increase oxygen, increased oxygen, oxygen supplementation, supplemental oxygen, oxygen saturation, oxygen administration, oxygen therapy,** Automated closed loop control, FIO2 automatic, FIO2 adjustment closed-loop, FIO2 control, ***compliance, complia*, nursing compliance, Adherence, adher****

+Keywords that were MeSH terms

The QualSyst tool for qualitative studies is a validated generic checklist consisting of ten items with scores from zero to two, with the maximum total score of 20. A summary score was calculated for each study by summing the total score across the ten items and dividing them by the total possible score of 20.[28] Data from selected studies were extracted using a data extraction form. The following study characteristics were extracted: author, year, design, sample, time points, length of measurement, TR and key results.

RESULTS

Sixteen articles met the inclusion criteria for this review (Figure 1), detailing studies that included a total of 574 infants and 2935 nurses. Fourteen of these studies used a quantitative design[18-20 29-39] while the remaining two used qualitative methods.[40 41] Pooling the data for meta-analysis was not possible, as there was no homogeneity in the study designs. We therefore discuss the studies and their results using a narrative format organised under thematic headings and summarised in tables.

Quality assessment

The studies varied in quality, but none were excluded because of low quality scores. One observed weakness was the lack of power analysis in four of the studies[18 19 30 32] and all studies were unclear in the reasoning behind the timing and duration of SpO_2 data collection (Table 2,3).[18-20 29-32 35-41]

Study Designs

The designs of the quantitative studies varied, and were composed of: one efficacy study [33]; two pilot clinical trials[39 42]; three randomised clinical trials[35 36 38]; and eight observational studies, of which six had a prospective design [18-20 29 30 37] and two were retrospective.[31 32] Both qualitative studies employed a descriptive design (Table 4). [40 41]

Target ranges of SpO_2

The lower limit of the TR varied between studies from 80-92%[19 38] and upper limits of TR varied from 92-96% respectively (Table 4).[18-20 30 31 33 37]

Time points and length of measurements

All studies were conducted in the period the infants needed supplemental oxygen, but the starting time points and duration of data collection differed between studies. The starting time point varied between the first day of life[37 40] and 33 days[34] (Table 4). In one study, the postnatal age was not described.[30] The duration of data collection also varied widely, the

shortest covering was only four hours[33] and the longest lasted the entire period between admission and discharge.[18] The data were collected continuously in eight studies[31-39] and intermittently in the remaining studies (Table 4).[18 19 29 30]

Table 2. Quality appraisal of included quantitative studies

Quality assessment quantitative studies															
Studies		2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	
	Question	Study design	Selection	Subject Characteristics	Random Allocation	Blinding Investigator	Blinding Subjects	Outcome	Sample Size	Analytic Methods	Estimate on variance	Confounding	Results	Conclusion	Summary score
Claure, N. *et al.* (2001)	1	1	1	2	1	0	n/a	1	n/a	2	2	1	1	1	14/24 = 0.58
Claure, N. *et al.* (2009)	1	1	1	2	1	0	n/a	1	2	2	2	1	1	1	16/26 = 0.62
Claure, N. *et al.* (2011)	2	2	2	2	1	0	0	2	2	2	2	1	2	2	22/28 =0.79
Clucas, L. *et al.* (2007)	2	2	1	2	0	0	0	2	0	2	2	1	2	2	18/28 = 0.64
Hagadorn, J.I *et al.* 2006)	2	2	1	2	1	0	0	1	0	2	2	1	1	1	16/28 = 0.57
Laptook, A.R. *et al.* (2006)	1	1	1	2	0	0	0	1	2	2	2	1	1	1	15/28 = 0.54
Mills, B.A. *et al.* (2010)	2	2	1	2	1	0	0	1	0	2	2	1	1	2	17/28 = 0.61
Sink, D.W. *et al.* (2011)	2	1	1	1	0	0	n/a	1	n/a	2	0	1	1	1	11/24 = 0.46
Urschitz, M.S. *et al.* (2004)	2	2	2	2	2	0	0	1	2	2	2	1	2	2	22/28 = 0.79
Van der Eijk, A.C. *et al.* (2012)	1	2	2	2	0	0	0	1	0	2	1	1	1	1	14/28 = 0.5
Zapata, J. *et al.* (2014)	2	2	2	2	2	0	0	2	1	2	2	1	2	2	22/28 = 0.79
Lim, K. *et al.* (2014)	2	2	2	2	n/a	n/a	n/a	2	n/a	2	2	2	2	2	20/20=1
Arawiran, J. *et al.* (2014)	2	2	2	2	n/a	n/a	n/a	1	1	2	2	1	2	1	18/22 = 0.82
Hallenberger, A. *et al.* (2014)	2	2	2	2	2	0	0	2	2	2	2	1	1	1	21/28 = 0.75

2 = yes; 1 = partial; 0 = no; n/a = not applicable

Table 3. Quality appraisal of included qualitative studies

Quality assessment qualitative studies											
Studies	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	
	Question objective	Study design	context	Theoretical framework	Sampling strategy	Data Collection	Data Analysis	Verification procedure	Conclusion	Reflexivity	Summary score
Nghiem, T.H. *et al.* (2008)	2	2	2	2	1	2	2	0	1	2	16/20 = 0.8
Armbruster, J. *et al.*. (2010)	1	2	2	2	2	2	0	0	2	2	15/20 = 0.75

2 = yes; 1 = partial; 0 = no

Compliance in target ranges

Twelve studies investigated how often SpO_2 values were in or outside the TR, expressed as the percentage of monitored time.[19 20 29 31-39] In a multi-centre study, Hagadorn *et al.* observed that SpO_2 was below, within or above TR in 16 (0-47)%, 48 (6-75)%, and 36 (5-90)% respectively of the monitored time.[19] Van der Eijk *et al*. reported similar values, finding that SpO_2 was below TR for 16 % of the time and above it for 30%.[32] In contrast, Lim *et al*. only studied infants receiving supplemental oxygen during Continuous Positive Airway Pressure (CPAP) and SpO_2 was below the TR for 9% and above it for 58% of the time.[20]

Education and training

Two studies demonstrated the impact of an educational program in targeting SpO_2. Laptook *et al*., observed that training did not change the time SpO_2 was below (26.9 vs. 26.6%; ns) or above TR (15.4 vs. 14.0%; ns).[29] Interestingly, Arawiran *et al*. even observed that training had an adverse effect, and that the time SpO_2 was within TR decreased after training (44.5 ± 14.4 % vs 40.4 ± 12.8 %) with an increase in time above TR (from 36.9 ± 17.2% vs 41.9 ± 15.6%).[37]

Nurse:patient ratio

Sink *et al*. studied the influence of the nurse:patient ratio on compliance in SpO_2 targeting. They observed that the proportion of time when SpO_2 was below TR decreased from 0.06 to 0.03 and time above TR increased from 0.56 to 0.82 when a third or fourth patient was

added to the nurse's workload.[31] The high percentage of time above TR was probably due to the use of a lower upper limit (92%) in comparison with other studies.[29 32-36] Lim *et al*. also confirmed that more than one infant per nurse was associated with an increase in the time when SpO_2 was above TR (Table 4).[20]

Automated regulation of inspired oxygen

Six recent studies reported that, compared to manual titration, the use of automated regulation of inspired oxygen increased the time SpO_2 spent within TR.[33-36 38 39] In a multicentre crossover study of ventilated preterm infants, Claure *et al.* observed that the time SpO_2 was within TR increased significantly during the automated period compared to the manual period (40% (14) vs 32% (13) (mean (SD);p<0.001). The time periods with SpO_2 >93% or >98% were thus significantly reduced during the automated period.[35] Although most studies observed that the time SpO_2 was above TR decreased[33-36 39] while the time below TR increased,[34-36 39] Hallenberger *et al.* found different results. They observed no change in time above TR (16 (0.0-60) vs 15.9 (1.9-34.8);p=0.108) during automatic control of inspired oxygen and therefore no difference with manual control (Table 4).[38]

Compliance in alarm limits setting

Two studies investigated nursing compliance in setting the appropriate alarm limits for PO in preterm infants.[18 30] The actual SpO_2 values were not reported, but Clucas *et al.* observed the lower and upper alarm limit to be set correctly in 91% and 23% of monitored time respectively.[18] Mills *et al.* compared compliance in alarm settings of SpO_2 according to whether or not infants participated in a trial. When infants were participating in the BOOST II trial the lower and upper alarm limit for SpO_2 was set correctly in 94% (88-100%) and 80% (71-88%) of the monitored time period. However, this decreased to 87% (75-99%) and 29% (17-40%) when infants were not participating in the trial (Table 4).[30]

Nurses' perception and awareness

When Armbruster *et al.* interviewed nurses about compliance, they stated that the following would improve their compliance: further education, prompt response to alarm limits, a favourable patient to staff ratio, root cause analyses at the bedside, and high priority given to control oxygen therapy.[40] Nghiem *et al*. reported that 63% of the nurses were aware of the local SpO_2 guidelines and 57% of them correctly identified the target limits specified by their NICU guidelines (Table 4).[41]

Table 4. Summary of included studies

Author	Year	Design	Study objects	Timing of measurement	Target range	Key results
Armbruster, J. *et al.*	2010	Qualitative study with Individual open-ended interviews	41 nurses	First three days of life while infants were receiving supplemental oxygen	88% - 92%	Saturations of infants in the COT- study (Canadian Oxygen Trial) were in the intended range in 68%-79% of time. Nurses identified education, prompt response to alarm limits, and a favourable patient to staff ratio as important determinants of good compliance
Claure, N. *et al.*	2009	Pilot clinical trial	16 premature infants, GA 24.9 ±1.4 weeks receiving mechanical ventilation and FiO_2 >0.21	Four hour period with FiO_2 adjustment by clinical staff members (manual) and 4-hour period with automated FiO_2 adjustments (automated) PNA 33 days (SD±15)	88% - 95%	**In automated mode:** • % of time within SpO_2 target range was 58% • % of time SpO_2 >95% was 9% • % of time SpO_2 <88% was 33% **In manual mode:** • % of time within SpO_2 target range was 42% • % of time SpO_2 >95% was 31% • % of time SpO_2 <88% was 27%
Claure, N. *et al.*	2001	Efficacy study	14 infants, GA 25 weeks (SD ±1.6) receiving mechanical ventilation and FiO_2 >0.21	two hours in manual FiO_2 mode and two hours in automatic FiO_2 mode in random sequence. PNA 26 days (SD±11)	88-96%	**In automatic FiO_2 mode** • % of time within SpO_2 target range was 74.9 % • the percentage of time saturations were < 88% was 16.5% and • >96% in 9.9% of the time. **In manual FiO_2 mode** • % of time within SpO_2 target range was 66.3% • the percentage of time saturations < 88% was 18.7% and • >96% in 14.9% of time.
Claure, N. *et al.*	2011	Clinical trial	32 premature infants GA 25 (24-27) wks receiving mechanical ventilation and FiO_2 >0.21	24 –hour period with FiO_2 adjustment by clinical staff members (manual) and 24-hour period with automated FiO_2 adjustments (automated) PNA 27 days (range 17-36)	87%-93%	**In automated mode:** • % of time within SpO_2 target range was 40% • % of time SpO_2 >93% was 28% • % of time SpO_2 <87% was 32% **In manual mode:** • % of time within SpO_2 target range was 32% • % of time SpO_2 >93% was 43% • % of time SpO_2 <87% was 23%

Clucas, L. *et al.*	2007	Prospective cohort study	80 infants with receiving supplemental oxygen mean GA of 28,4 weeks (SD ±2.4) 1073 lower and upper alarm limit values	Daily during weekdays, when the infant was on oxygen until discharge PNA five days (IQR 2-34.5)	88% -92%	The lower alarm limit was set correctly in 91.1% of the time, 6.3% was set lower and 2.7% were set higher than intended; Upper alarm limit was set correctly in 23.3% of the time, 0.2% was set lower and 76.5% were set higher than intended.
Hagadorn, J.I. *et al.*	2006	Prospective multi-centre cohort study	84 infants GA 26.3 Median: (29.4 - 27,4) 14 centres from three counties 307 monitor periods of median duration of 67.3 hours	Saturation for 72 hours each week for the first four weeks of life	Center specific Intended TR 92–96% 90–95% 88–95% 88–97% 88–92% 87–94% 92–96% 90–96% 85–98% 88–94% 85–94% 88–92% 83–93%	Overall, infants spent 16% below intended range and 36% above their NICUs intended range
Laptook, A.R. *et al.*	2006	Prospective observational study	Group 1: 23 infants GA 27 weeks (± 2) receiving continuous supplemental oxygen (with or without ventilator) group 2: 49 infants, GA 26 weeks (± 2) receiving continuous supplemental oxygen (with or without ventilator)	24 hours of data twice a month during six months when the author was available PNA group 1: 23 days (±21) PNA group 2: 23 days (±19)	Group 1: target range 90-95%, Group 2: target range: 88-94%	**Group 1:** SpO_2 values were under target range in 26.9% and above the target range in 15.4 % of time **Group 2:** SpO_2 values were under target range in 26.6% and above the target range in 14.0 % of time
Mills, B.A. *et al.*	2010	Prospective cohort study	56 infants mean GA 26.7 wks (SD 2.0) receiving supplemental oxygen 22 infants in BOOST II trial Number of recordings = 454	Daily during weekdays, when the infant was on oxygen until discharge	88% - 92%	**Lower alarm limits:** In BOOST II trial; 94.2% was set correctly; not in BOOST II; 87.3 % was set correctly. **Upper alarm limits:** In BOOST II trial; 79.8% was set correctly; not in BOOST II; 28.8% was set correctly

Nghiem, T.H. *et al.*	2008	Survey	59 NICUs 2805 nurses who submitted surveys	First four weeks of life of preterm infants	68% of included NICUs, had policy specified SpO_2 target limits; not exactly defined	Of 1957 nurses at NICUs with policies; 64% of nurses were aware that policy for SpO_2 was present in their NICU. 715 (37%) nurses correctly identified the SpO_2 limits specified by their NICU policy
Sink, D.W. *et al.*	2011	Retrospective observational study	14 infants GA < 26.6 (SD±1.6) weeks with oximeter data 87 nurses	Every two seconds during routine bedside oximetry monitoring PNA 31.6 weeks (mean range 24.1-40.7 weeks)	85% - 92%	SpO_2 in infants <28 GA were 61% above intended range and 6% under de intended range. Infants of 28-31 weeks gestation were 70% above intended range and 7% under de intended range. Hyperoxaemic time increased from 48% to 71% with assignment of a second patient to the infant's nurse and to 82% with assignment of a third patient to the infant's nurse
Urschitz, M.S. *et al.*	2004	Randomized controlled clinical trial (Validation and efficacy trial)	**Validation trial:** 12 preterm infants GA; Median (IQR)24.5 (24-28) receiving ventilator support and FiO_2 >0.21 **Efficacy trial;** 12 preterm infants GA; median (IQR) 25.5 (24-33) receiving ventilator support and FiO_2 >0.21	one day during five periods of different modes, 90 minutes in each mode • Baseline 1, • Routine Manual control, • Optimal Manual Control, • Closed-loop Control, • Baseline 2 **Validation trial:** PNA 21 days (median range 8-57) **Efficacy trial;** PNA 20.5 days (median range 4-78)	87-96%	**Validation trial:** % of time within SpO_2 target range was: • Baseline 1, 75.3% • Routine Manual control, 79.7% • Optimal Manual Control, 85.8% • Closed-loop Control, 82.1% • Baseline 2, 79.4% No information on hypoxaemic and hyperoxaemic periods **Efficacy trial:** % of time within SpO_2 target range was: • Baseline 1, 82.9% • Routine Manual control, 81.7% • Optimal Manual Control, 91% • Closed-loop Control, 90.5% • Baseline 2, 81,2% **duration of hypoxaemic episodes** • Baseline 1, 20.2s (11.3%) • Routine Manual control, 19s (10.7%) • Optimal Manual Control, 16.4s (9.2%) • Closed-loop Control, 12.4s (7%) • Baseline 2, 19.1s (10.7%)

						duration of hyperoxaemic episodes • Baseline 1, 24.7s (6.7%) • Routine Manual control, 19.3 s (5.2%) • Optimal Manual Control, 16.4s (5%) • Closed-loop Control, 10.1s (2.7%) • Baseline 2, 17.4s (4.7%)
Van der Eijk, A.C. *et al.*	2012	Observational cohort study	12 infants, median GA 26 2/7 weeks (range24 2/7 -28) with a need for supplemental oxygen	Recording started when FiO_2 was >0.21 in the first two weeks op life PNA four days (range 2-12)	88%-94%	SpO_2<88% in 16% of the time and >94% in 30% of the time
Zapata, J. *et al.*	2014	Pilot clinical trial	20 infants, mean GA 27.3±1.7 vs 27.7±1.7 weeks receiving supplemental oxygen by nasal cannula	12 hour study period PNA 5-14 days	85%-93%	**With automixer:** • % of time within SpO_2 target range was 58% • % of time SpO_2 >95% was 26.5% • % of time SpO_2 <85% was 14% **In manual routine care:** • % of time within SpO_2 target range was 33.7% • % of time SpO_2 >95% was 54.8% • % of time SpO_2 <85% was 11.5%
Hallenberger, A. *et al.*	2014	Multicente randomised controlled crossover clinical trial	34 infants median GA (range) 26.4 (23.0–35.3) receiving mechanical ventilation or nasal CPAP and supplemental oxygen	24 hour period with routine manual control (RMC) and 24 hour period with closed loop automated control (CLAC) PNA 29.9 (26.0–35.6) weeks (median (range))	4 centre-specific TR 90–95% 80–92% 83–93% 85–94%	**In closed loop automated control (CLAC):** • % of time within SpO_2 target range was 72.1 (13.6) (mean(SD)) • % of time SpO_2 above TR was 15.9 (1.9–34.8) (median (range)) • % of time SpO_2 below TR was 9.1 (1.9–24.2) (median (range)) **In routine manual control (RMC)** • % of time within SpO_2 target range was 61.0 (15.2) (mean(SD)) • % of time SpO_2 above TR was 16.0 (0.0–60.0) (median (range)) • % of time SpO_2 below TR was 15.0 (0.5–39.6) (median (range))

Arawiran, J. *et al.*	2014	Prospective observational cohort study	71 premature infants GA <31 weeks **Pre-intervention phase:** 41 infants: 25 ± 1.6 weeks (mean ± SD) **Post-intervention phase:** 30 infants: 25 ± 1.9 weeks (mean ± SD)	Study period from first day of life as long as they received supplemental oxygen or were taken off the Masimo monitors or reached 31 weeks postconceptual age, whichever occurred first	85% - 92%	**Pre-intervention phase:** • Proportion of time spent per 12-h shift in which individual babies were (mean(%)±SD(%)) • <70% was 3.4 ± 2.6 • 70–74% was 1.6 ± 1.3 • 75–79% was 4.0 ± 2.9 • 80–84% was 9.6 ± 5.63 • 85–92% was 44.5 ± 14.4 • 93–100% was 36.9 ± 17.2 **Post-intervention phase:** • Proportion of time spent per 12-h shift in which individual babies were (mean(%)±SD(%)) • <70% was 3.3 ± 2.5 • 70–74% was 1.6 ± 1.1 • 75–79% was 3.9 ± 2.3 • 80–84% was 8.9 ± 4.3 • 85–92% was 40.4 ± 12.8 • 93–100% was 41.9 ± 15.6
Lim, K. *et al.*	2014	Multicentre prospective observational cohort study	45 premature infants GA 30 (IQR 27-32 weeks) 2971 hours receiving supplemental oxygen	Age at first recording was at day one (IQR 0-8 days)	88% - 92%	median (IQR) proportion of time in % • % of time within SpO_2 target range was 31 (19-39)% • % of time SpO_2 >93% was 59 (36-74) % • % of time SpO_2 <87% was 9 (4.3-18)% more than one infant per nurse was associated with a greater frequency of significant hyperoxaemia (SpO_2 >98%) when infants were in supplemental oxygen and a trend towards less eupoxaemia

DISCUSSION

The wide variation in study methodologies made it necessary to use narrative reporting when discussing the results of this systematic review. Although the power of some of the studies was limited and the quality varied, all were considered eligible for inclusion. Moreover, they focused on different aspects of compliance in targeting SpO_2. The design, TR of SpO_2, time points and duration of each study differed.

The central finding is that compliance in targeting SpO_2 was low, as were the alarm settings. All studies in compliance in oxygen targeting reported that maintaining the SpO_2 below the upper limit was the most difficult to adhere to.[18-20 30-32 35 37-39 42] The analysis of the large clinical trials comparing lower vs higher SpO_2 TR was based on the intention to treat principle. However, the larger proportion of the SpO_2 was either below or above the intended TR and there was also an overlap between the two TRs.[25 43 44] Although compliance was audited[30], it is possible that this has influenced the outcome of the trials. This underlines the importance in improving compliance in targeting SpO_2, as improved compliance could have influenced the results.

According to the studies

Several factors may play a role in low compliance in targeting SpO_2: lack of awareness of the TR settings, limited knowledge of the effects of hypoxaemia and hyperoxaemia, and an increased nurse:patient ratio.[20 31 40 41 45] Many caregivers were unaware of the appropriate SpO_2 limits.[41] In addition, nurses tend to rely on subjective observations for oxygen titration, such as skin color and chest excursions, as well as on PO and blood gases.[46] So far, studies indicate that the effects of education and training in improving the compliance targeting SpO_2 are disappointing.[37 45]

On the other hand, the use of automated fraction of inspired oxygen (FiO_2) regulation, which eliminates the need for the nurses' compliance, has been shown to improve the time SpO_2 remains within TR.[33-36 39] The increase in time within TR was small, but it is possible that the effect of automated FiO_2 regulation has been underestimated. A Hawthorne effect could have increased the nurses' compliance during the short study period, thus decreasing the difference between the manual and automated periods. The effectiveness of automated regulation on oxygenation variability, and whether this results in an improved outcome, remains to be investigated.[47]

It has been suggested that the absence of a FiO_2 titration protocol leads to saturations which would frequently exceed or fall below the TR.[48] Manual adjustments of FiO_2 can vary widely in frequency and step size, so standardization of these adjustments could decrease large fluctuations in SpO_2.[32] After implementing an oxygen titration protocol for reducing the incidence of severe ROP, Lau *et al.* observed that the period during which SpO_2 was above TR decreased significantly.[48]

Although fewer studies investigated this, compliance with alarm settings appeared to be low as well, especially the upper alarm limit.[18 30] In addition, even when alarm limits are appropriately set, caregivers seem to have a preference for SpO_2 close to the upper alarm limit.[13 44] This was also demonstrated in the large trials comparing TR of SpO_2.[25] It is possible that caregivers are more accustomed to prevent hypoxaemia than hyperoxaemia. It is also possible that infants are more stable in SpO_2 when kept at the higher end of the TR. A regular check of alarm limit settings each shift could increase awareness of this issue.

Educational programs on hyperoxaemia improved knowledge levels,[49 50] but did not lead to better compliance. Earlier research has shown that after education in risks related to hyperoxaemia the nurses' performance was still variable and only 51% of nurses were successful in minimising exposure of their infants to hyperoxaemia.[51] Nurses usually take care of more than one patient and perform multi-tasking[52] and an increased workload decreases their compliance in TR.[20 31] Also, nurses frequently have to deal with alarms, but a large proportion of the alarms are false.[53] The common occurrence of false alarms or "cry wolf" phenomenon could lead to no or delayed response of caregivers.

The decision not to limit inclusion criteria in terms of study design and methodology led to a high level of variety within the chosen studies, necessitating a narrative review. The advantage of this method, however, is that it enabled us to have a complete overview of a range of different aspects related to compliance in targeting SpO_2. However, the review was restricted to recent studies published in English and Dutch; similar studies published in other languages may have been missed. In addition, the selection process was conducted by the first author only and selection bias could have occurred.

In conclusion, the main finding of this literature review is that there is a low compliance in SpO_2 targeting and alarm settings during oxygen therapy in preterm infants, especially in maintaining the SpO_2 below the upper limit and in setting the upper alarm limit. Although there is little data available, it is likely that training, titration protocols, and decrease of the nurses' workload could improve awareness and compliance. Automated oxygen regulations have been shown to increase the time SpO_2 remains within the TR. Improving the compliance in targeting SpO_2 and automated control has the potential to improve the outcome in preterm infants, but this needs further investigation.