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SYSTEMATIC REVIEW

Normal regional tissue oxygen saturation in neonates: a systematic qualitative review

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BACKGROUND: The aim of this systematic qualitative review was to give an overview of reference ranges defined as normal values or centile charts of regional tissue oxygen saturation measured by near-infrared spectroscopy (NIRS) in term and preterm neonates.
METHODS: A systematic search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials was performed. Additional articles were identified by manual search of cited references. Only human studies in neonates were included.
RESULTS: Nineteen studies were identified. Eight described regional tissue oxygen saturation during fetal-to-neonatal transition, six during the first 3 days after birth, four during the first 7 days after birth, and one during the first 8 weeks after birth. Nine described regional tissue oxygen saturation in term, nine in preterm neonates, and one in both. Eight studies published centile charts for cerebral regional tissue oxygen saturation, and only five included large cohorts of infants. Eleven studies described normal values for cerebral, muscle, renal, and abdominal regional tissue oxygen saturation, the majority with small sample sizes. Four studies of good methodological quality were identified describing centile charts of cerebral regional tissue oxygen saturation.
CONCLUSIONS: In clinical settings, quality centile charts are available and should be the preferred method when using NIRS monitoring.

Pediatric Research; https://doi.org/10.1038/s41390-021-01786-y

IMPACT:

- Near-infrared spectroscopy (NIRS) enables a bed-side non-invasive continuous monitoring of tissue oxygenation.
- When using NIRS monitoring in a clinical setting, centile charts with good quality are available and should be preferred to normal values.
- High-quality reference ranges of regional tissue oxygenation in term and preterm born neonates are an important step toward routine clinical application of NIRS.

INTRODUCTION

More than 7% of newborn infants born in the United States are admitted to the neonatal intensive care units for monitoring, stabilization, and care after birth.[1] Non-invasive monitoring of arterial oxygen saturation, heart rate, respiratory rate, and/or blood pressure is the standard.[2] Additionally, non-invasive monitoring of temperature, pCO_2, pO_2, and cerebral activity is also widely used. The aim of neonatal intensive care and monitoring is to achieve adequate organ perfusion and oxygenation, prevent injury, and enable normal neurodevelopment in critically ill neonates. However, none of the routine non-invasive monitoring methods provide information on regional tissue oxygen saturation, oxygen delivery, and oxygen consumption.

Near-infrared spectroscopy (NIRS) continuously assesses regional tissue oxygen saturation non-invasively.[3] NIRS enables monitoring of tissue oxygenation and perfusion in regions of interests, including the brain, peripheral muscle, abdomen, and/or kidney.[3] In preterm neonates, cerebral NIRS monitoring combined with a treatment protocol was investigated in two randomized controlled trials and reduces the burden of hypoxia and hyperoxia and might also affect morbidity and mortality.[4,5] Several studies have defined normal values (mean [standard deviation] or median [range]) or established centile charts (values below which a given percentage of neonates fall).[6–24] However, these may vary depending on device, sensor, study population, and/or measured body sites.[25–27] Robust reference values and associated variations of the regional tissue oxygen

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Received: 23 February 2021 Revised: 21 September 2021 Accepted: 22 September 2021
Published online: 20 October 2021

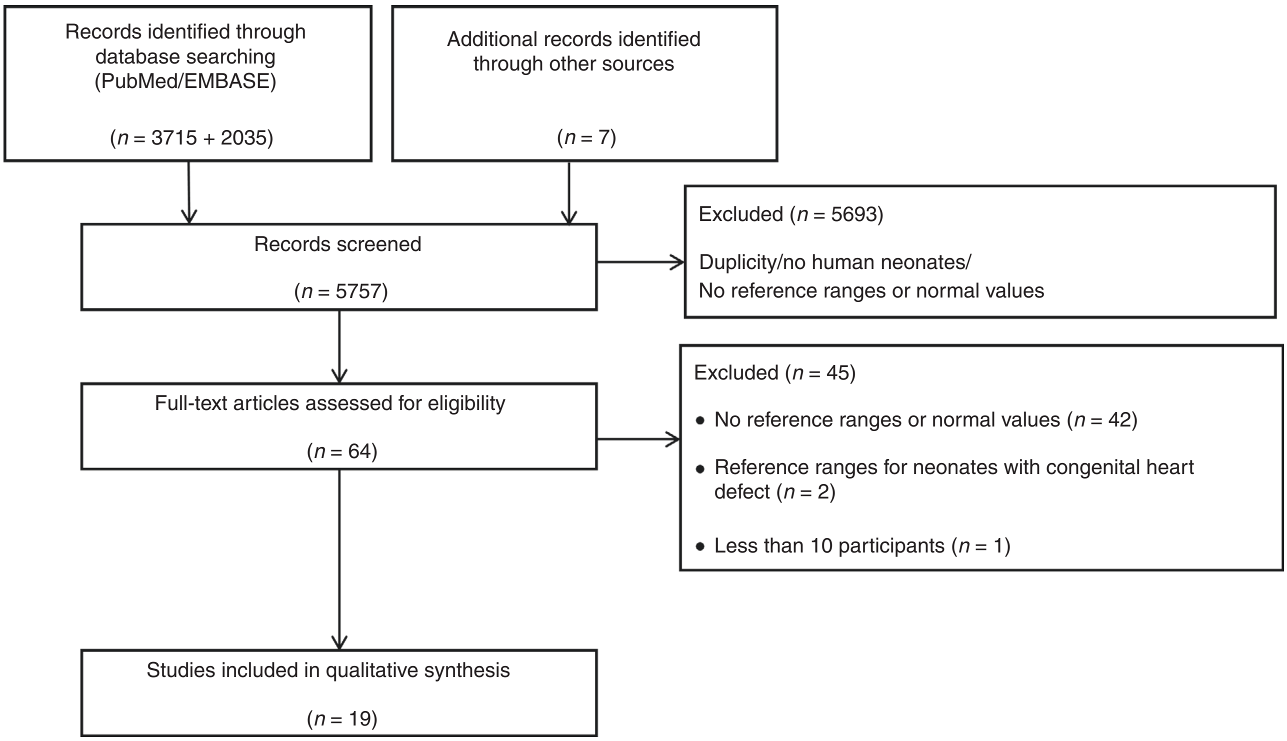

Fig. 1 Flow diagram.

saturation measured by NIRS need to be firmly established before routine clinical adoption can be implemented in neonates. Accordingly, the aim of this study was to perform a systematic qualitative review of available reference ranges defined as (i) normal values or (ii) centile charts of regional tissue oxygen saturation measured by NIRS in term and preterm neonates.

METHODS

Articles were identified using the stepwise approach specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement.[28] The systematic review was registered in PROSPERO (CRD42020180408).

Search strategy

We searched the following electronic databases: MEDLINE (through PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) using a predefined algorithm (see Appendix A), with the included search terms newborn, infant, neonate, preterm, term, near-infrared-spectroscopy, NIRS, oximetry, spectroscopy, tissue, muscle, brain, cerebral, peripheral, kidney, renal, arm, calf, abdomen, liver, flank, reference, normal, percentile, centile, and range. Additional published reports were identified through a manual search of references in the retrieved original manuscripts and review articles. We also reviewed abstracts from relevant meetings. No language restrictions were applied and we searched from March 1964 through April 2021.

In the present systematic review, we included studies in which reference ranges for regional tissue oxygen saturation were defined as normal values or determined from centile charts. In term neonates, we included only studies reporting on healthy neonates without any need for medical support. In preterm neonates, we included all studies in which reference ranges for regional tissue oxygen saturation were defined as normal values or centile charts, since especially very low birth weight neonates are all in need of medical support. Studies including neonates with congenital anomalies (e.g., heart defects, genetic abnormalities) or studies with a sample size below ten neonates were excluded. Only human studies providing normal values or centile charts of regional tissue oxygen saturation were included.

Study selection

Two reviewers (M.B. and C.H.W.) independently assessed the title and abstract of studies for eligibility. Full texts were retrieved and were included based on the eligibility criteria. Any disagreement was resolved through discussion and consensus between three authors (M.B., C.H.W., and G.P.), who critically appraised the full text of the identified articles and assessed the methodological quality of the included studies. Primary outcome measures were reference ranges defined as (i) normal values and/or (ii) centile charts of regional tissue oxygen saturation. Normal values of tissue oxygen saturation had to be expressed as mean (standard deviation) or median (range), whereas centiles of the tissue oxygen saturation (charts) had to indicate values below which a given percentage of neonates fall. Data extraction was performed using a standardized collection form, which included study design and methods, patient characteristics, and results. One investigator (M.B.) extracted data and resolved discrepancies in consultation with another member of the review team (G.P.). Permission to reuse figures was obtained from the authors and the original publishing journal.

Assessment of methodological quality

The methodological quality of the included studies was evaluated by using the following domains: (i) sample size, (ii) continuity and duration of the measurements, (iii) use of reapplication, (iv) specification of the used sensor, and (v) definition of quality criteria to detect and eliminate artifacts.

RESULTS

The primary search identified 5757 articles: 3715 articles were identified in PubMed, 2035 articles in EMBASE, 0 in CENTRAL, and 7 articles through other sources. After title and abstract screening, the full text of 64 relevant studies was assessed and 19 studies met the

Table 1. Characteristics of the studies including term neonates.

Author (Ref.)	Neonates (*n*)	Gestational age (weeks)	Medical support	Study aim	Device	Body site	Values	Normal values (%)[a] 50th Centile (%)	NIRS position	Age at assessment
Fetal-to-neonatal transition										
Xue et al.[14]	230	≥ 37	No	Centile charts	FORE-SIGHT (neonatal sensor)	Cerebral	cSO_2	Min 2—49.0 Min 5—64.5 Min 10—74.0 Min 30—82.0 Min 60—81.0	Forehead left	First hour after birth
Ozawa et al.[20]	127	≥ 37	No	Centile charts	Toccare KN-15	Cerebral	$CrSO_2$	Min 1—~45 Min 5—~52 Min 10—~56	Forehead left	First 10 min after birth
Kato et al.[21]	88	34–42	No	Centile charts	Toccare KN-15	Cerebral	$CrSO_2$	Min 1—~42 Min 5—~52 Min 10—~56	Forehead	First 10 min after birth
Montaldo et al.[15]	61	≥ 37	No	Normal values	EQUANOX 7600	Cerebral Renal Abdominal	$CrSO_2$ $RrSO_2$ $MrSO_2$ CtFOE RtFOE MtFOE	See ref. 4	Forehead, posterior flank, infra-umbilical abdomen	First 9 h after birth
Baik et al.[7]	140	≥ 37	No	Centile charts	NIRO 200 NX	Cerebral	CTOI cFTOE	Min 1—N/A Min 5—66 Min 10—75	Forehead right	First 15 min after birth
Pichler et al.[6]	354	≥ 37	No	Centile charts	INVOS 5100c (neonatal sensor)	Cerebral	$CrSO_2$ cFTOE	Fig. 4	Forehead left	First 15 min after birth
Fauchère et al.[17]	20	≥ 37	No	Centile charts	NIRO 300	Cerebral	CTOI cFTOE	Min 1—N/A Min 5—~65 Min 10—~70	Forehead right	First 15 min after birth
First 3 postnatal days										
Roerdink et al.[22 b]	159	34–42	No	Normal values	INVOS 4100c (adult sensor) NIRO 200NX	Cerebral	$CrSO_2$	INVOS—84 (6) NIRO—70 (7)	Forehead	First 36 h after birth
						Muscle	$MrSO_2$	INVOS—92 (5) NIRO—78 (6)	Thigh	
Bailey et al.[23]	38	≥ 37	No	Normal values	INVOS 5100c (sensor unknown)	Cerebral	$CrSO_2$	Day 1—78.2 (7.9) Day 2—78.3 (6.1)	Forehead left	First 2 postnatal days
						Renal	$RrSO_2$	Day 1—92.1 (5.3) Day 2—88.9 (5.9)	Back right	
						Abdominal	$SrSO_2$	Day 1—69.9 (12.1) Day 2—75.3 (12.4)	Abdomen left	

Table 1 continued

Author (Ref.)	Neonates (*n*)	Gestational age (weeks)	Medical support	Study aim	Device	Body site	Values	Normal values (%)[a] 50th Centile (%)	NIRS position	Age at assessment
First 7 postnatal days										
Bernal et al.[24]	26	≥37	No	Normal values	INVOS 5100b (pediatric sensor)	Cerebral	RSO_2C	76.8 (8.5)	Forehead	First 120 h after birth
						Renal	RSO_2R	86.8 (8.1)	Right flank	

$CrSO_2$/RSO_2C cerebral regional tissue oxygen saturation, *cFTOE* cerebral fractional tissue oxygen extraction, *min* minute, *$MrSO_2$* muscle regional tissue oxygen saturation, *N/A* not available, *$RrSO_2$/RSO_2R* renal regional tissue oxygen saturation, *$SrSO_2$* abdominal somatic regional tissue oxygen saturation.
[a]Normal values are expressed as mean (SD).
[b]Published as abstract at the conference meeting.

inclusion criteria (Fig. 1). A summary of the included studies is presented in Tables 1 and 2. Methodological quality of the included studies is presented in Figs. 2 and 3.

Centile charts

Eight studies described centile charts for cerebral regional tissue oxygen saturation.[6,7,14,17–21] However, only five of the eight studies described centile charts in large cohorts ($n > 100$) of term and preterm neonates.[6,7,14,19,20] There are no centile charts published in term or preterm neonates for muscle, renal, and abdominal regional tissue oxygen saturation.

Normal values

Normal values are available for cerebral, muscle, renal, and abdominal regional tissue oxygen saturation in term and preterm neonates.[8–13,15,16,22–24] The study by van der Heide et al. is the only one describing normal values with a sample size of >100 neonates,[9] another one has been published only as an abstract at a conference meeting.[22]

Fetal-to-neonatal transition

Seven studies were identified reporting centile charts of cerebral regional tissue oxygen saturation.[6,7,14,17,18,20,21] One study reported on normal values of cerebral, renal, and mesenteric regional tissue oxygen saturation from birth to 9 h after birth.[15] Five studies described centile charts for term neonates,[7,14,17,20,21] one study for preterm neonates,[18] and one study included both term and preterm neonates (Fig. 4).[6] One study described centile charts from min 2 to 1 h after birth[14] and 5 studies from min 2 to min 15.[6,7,17,20,21] There are no centile charts for muscle, renal, and abdominal regional tissue oxygen saturation and no normal values for muscle regional tissue oxygen saturation in neonates during fetal-to-neonatal transition published.

First 3 postnatal days

We identified 6 studies describing centile charts ($n = 1$) or normal values ($n = 5$) for the brain,[8,19,22,23] muscle,[11,12,22] renal, and abdominal[23] regional tissue oxygen saturation over this time period. Two studies described normal values for term or near term neonates,[22,23] one study described centile charts for preterm neonates (Fig. 5),[19] and three studies described normal values for preterm neonates.[8,11,12]

There are centile charts published for cerebral regional tissue oxygen saturation in preterm but not in term neonates during the first 3 days after birth. Furthermore, no centile charts for muscle, renal, and abdominal regional tissue oxygen saturation are available in the literature, neither in term nor in preterm neonates, during the first 3 days after birth.

First 7 postnatal days

A total of four studies described normal values of cerebral,[24] renal,[16,24] and abdominal[9,10] regional tissue oxygen saturation. One of these studies described normal values in more than one body site[24] and normal values for term neonates[24] and three studies described normal values for preterm neonates.[9,10,16]

There are no centile charts published for cerebral regional tissue oxygen saturation neither in term nor in preterm neonates for the first 7 days after birth. Furthermore, no centile charts are available in the literature for muscle, renal, and abdominal regional tissue oxygen saturation, neither in term nor in preterm neonates.

First 8 weeks after birth

We identified one study describing normal values for cerebral and abdominal tissue oxygen saturation for the first 8 weeks after birth in preterm infants born < 30 weeks of gestation.[13] There are no centile charts published for any other region over the first 8 weeks after birth.

Table 2. Characteristics of the studies including preterm neonates.

Author (Ref.)	Neonates (*n*)	Gestational age (weeks)	Medical support	Study aim	Device	Body site	Values	Normal values (%)[a] 50th Centile (%)	NIRS position	Age at assessment
Fetal-to-neonatal transition										
Pichler et al.[6]	27	<37	No	Centile charts	INVOS 5100c (neonatal sensor)	Cerebral	CrSO cFTOE	Fig. 4	Forehead left	First 15 min after birth
Fuchs et al.[18]	51	28 (SD 2.6)	Yes	Centile charts	FORE-SIGHT	Cerebral	$CStO_2$	Min 1—37 Min 5—~72 Min 10—~79	Forehead	First 10 min after birth
First 3 postnatal days										
Wolfsberger et al.[11]	100	<37	Yes	Normal values	NIRO 200	Muscle	pTOI pFOE	Time periods (h) 0–6—70 (68–75) 7–12—72 (67–76) 13–18—73 (70–75)) 19–24—70 (65–75)	Forearm right	First 24 hours after birth
Hoeller et al.[12]	87	<37	Yes	Normal values	NIRO-200NX	Cerebral	cTOI	Hour 4—71.0 (10.5) Hour 14—68.6 (11.7) Hour 24—70.1 (10.3)	Forehead left	First 30 hours after birth
							Muscle	pTOI	Hour 4 73.8 (6.8) Hour 14 73.8 (7.9) Hour 24 71.9 (7.1)	Forearm right
Alderliesten et al.[19]	999	<32	Yes	Centile charts	INVOS 4100 INVOS 5100c (adult sensor)	Cerebral	CrSO cFTOE	Fig. 5	Forehead	First 72 hours birth
Naulaers[8]	15	<31	Yes	Normal values	NIRO 300	Cerebral	CTOI	Day 1—57.0 (54.0–65.7) Day 2—66.1 (61.9–82.2) Day 3—76.1 (67.1–80.1)	Forehead right	First 3 postnatal days
First 7 postnatal days										
Harer et al.[16]	32	<32	Yes	Normal values	INVOS 5100c (neonatal sensor)	Renal	$RrSO_2$	Day 2—62.5 (57–65.7) Day 4—59.1 (57–59.9) Day 7—60.3 (57.8–66.9)	Right or left flank	Day 2 to day 7 after birth
Van der Heide et al.[9]	220	<32	Yes	Normal values	INVOS 5100c (neonatal sensor)	Abdominal	$RintSO_2$	Day 1—48.2 (16.6) Day 4—38.7 (16.6)	Infraumbilical	First week after birth

Table 2 continued

Author (Ref.)	Neonates (n)	Gestational age (weeks)	Medical support	Study aim	Device	Body site	Values	Normal values (%)[a] 50th Centile (%)	NIRS position	Age at assessment
								Day 7—44.2 (16.6)		
Patel et al.[10]	78	<32	Yes	Normal values	InSpectra 650	Abdominal	StO_2	Day 1—73.8 (1.8) Day 3—80.0 (1.4) Week 1—77.3 (14.4)	Right lower abdomen	First week after birth
First 8 postnatal weeks										
Howarth et al.[13 b]	43	<30	Yes	Normal values	NIRO 300	Cerebral	cTOI cFTOE	Week 1—65.4 Week 4—60.1 Week 8—56.8	Forehead	First 8 weeks after birth

$CrSO_2$/$CStO_2$ cerebral regional tissue oxygen saturation, *cTOI* cerebral tissue oxygen index, *cFTOE* cerebral fractional tissue oxygen extraction, *min* minute, *N/A* not available, *pTOI* peripheral tissue oxygen index, *pFOE* peripheral fractional oxygen extraction, *sTOI* abdominal somatic tissue oxygen index, *sFOE* abdominal somatic fractional oxygen extraction, *StO_2/$RintSO_2$* abdominal somatic regional tissue oxygen saturation.

[a]Normal values are expressed as mean (SD) or median (95% confidence interval) or median (interquartile range).

[b]Published as abstract at the conference meeting.

DISCUSSION

This is the first systematic qualitative review, which provides an overview of the available literature on reference ranges defined as normal values or centile charts of regional tissue oxygen saturation measured with NIRS in term and preterm neonates. Defining the reference ranges of regional tissue oxygenation in term and preterm born neonates is an important step in using these ranges as end points and surrogates for outcomes.

Fetal-to-neonatal transition

In term neonates, the published centile charts by Ozawa et al.,[20] Baik et al.,[7] Pichler et al.,[6] and Xue et al.[14] appear adequate regarding their sample size and study design. In contrast, Fauchère et al.[17] defined centile charts with only 20 infants, and therefore this study should be interpreted with caution. Whereas Baik et al.,[7] Fauchère et al.,[17] and Xue et al.[14] included exclusively neonates born by cesarean section, Ozawa et al.[20] and Pichler et al.[6] included both vaginally delivered and cesarean section delivered neonates and published centile charts regarding birth mode (Fig. 4). Furthermore, Pichler et al.[6] and Xue et al.[14] reported in detail which quality criteria were used to detect and eliminate artifacts for regional tissue oxygen saturation measurements. Interestingly, Xue et al.[14] reported on centile charts of cerebral tissue oxygen saturation in term neonates without medical support and in whom mothers received non-oxygen-inhaled intrathecal anesthesia. Ozawa et al.[20] and Kato et al.[21] used the Toccare KN-15 oximeter, a novel small portable NIRS device with a diagnostic finger-mounted oximeter, which was developed for the non-invasive measurement of fetal cerebral tissue oxygenation during labor.[29] The distance between the optical source and detector in this device is smaller than in other conventional NIRS devices, allowing the measurement at a depth of 0–5 mm.[20,21] This raises concerns that only the surface layer and not the brain tissue was measured when using the finger-mounted oximeter.[20] Montaldo et al.[15] published normal values for cerebral, renal, and mesenteric regional oxygen saturation. In their study, they including only a sample size of 61 term neonates and measurements were performed during the first 9 h after birth.[15] In a study on preterm neonates, Fuchs et al.[18] included neonates on nasal continuous positive airway pressure with a positive end-expiratory pressure of 5 cmH_2O and an initial FiO_2 of 0.4. If the heart rate remained < 100 beats per minute or arterial oxygen saturation remained < 70% without increase, up to three sustained inflations were applied for lung recruitment at increasing pressures (20, 25, 30 cmH_2O) for 15 s each. In contrast, Pichler et al.[6] included only preterm neonates without need for medical (respiratory or cardio-circulatory) support, which resulted in a small sample size ($n = 27$) and a higher gestational age. However, this is the only study describing centile charts of cerebral regional tissue oxygen saturation in preterm neonates without any need for respiratory support. Another limitation of the available reference ranges of tissue oxygenation during immediate transition is that in most neonates early cord clamping was performed.

First 3 postnatal days

The study including the largest sample size ($n = 159$) of term neonates has been published only as an abstract at a conference meeting.[22] Following personal communication with the senior author, the most stable 15 min measurements were selected from 30-min measurements. Data within two standard deviations were defined as stable. The main strengths are the large sample size and the used quality criteria; however, the limitation was that the non-continuous measurements during the first 3 days (30 min periods) were used. Bailey et al.[23] described normal values of cerebral, renal, and abdominal regional tissue oxygen saturation in term neonates. Although the sample size was small ($n = 38$), regional tissue oxygen saturation was recorded only every 30 s over a 1-h time period per day on the first and second day after

Fig. 2 Methodological quality criteria of studies in term infants. Sample size (red: $n = 10–50$, yellow: $n = 50–100$, green: $n > 100$); duration of the measurements (red: < 1 h per measurement period, yellow: 1–8 h per measurement period/non-continuous measurement during transition period, green: continuous measurement during study period); reapplication (red: no/not mentioned); specification of the used sensor (red: no, X: not applicable, green: yes); definition of quality criteria to detect and eliminate artifacts (red: not defined, yellow: sparely defined, green: reported in detail).

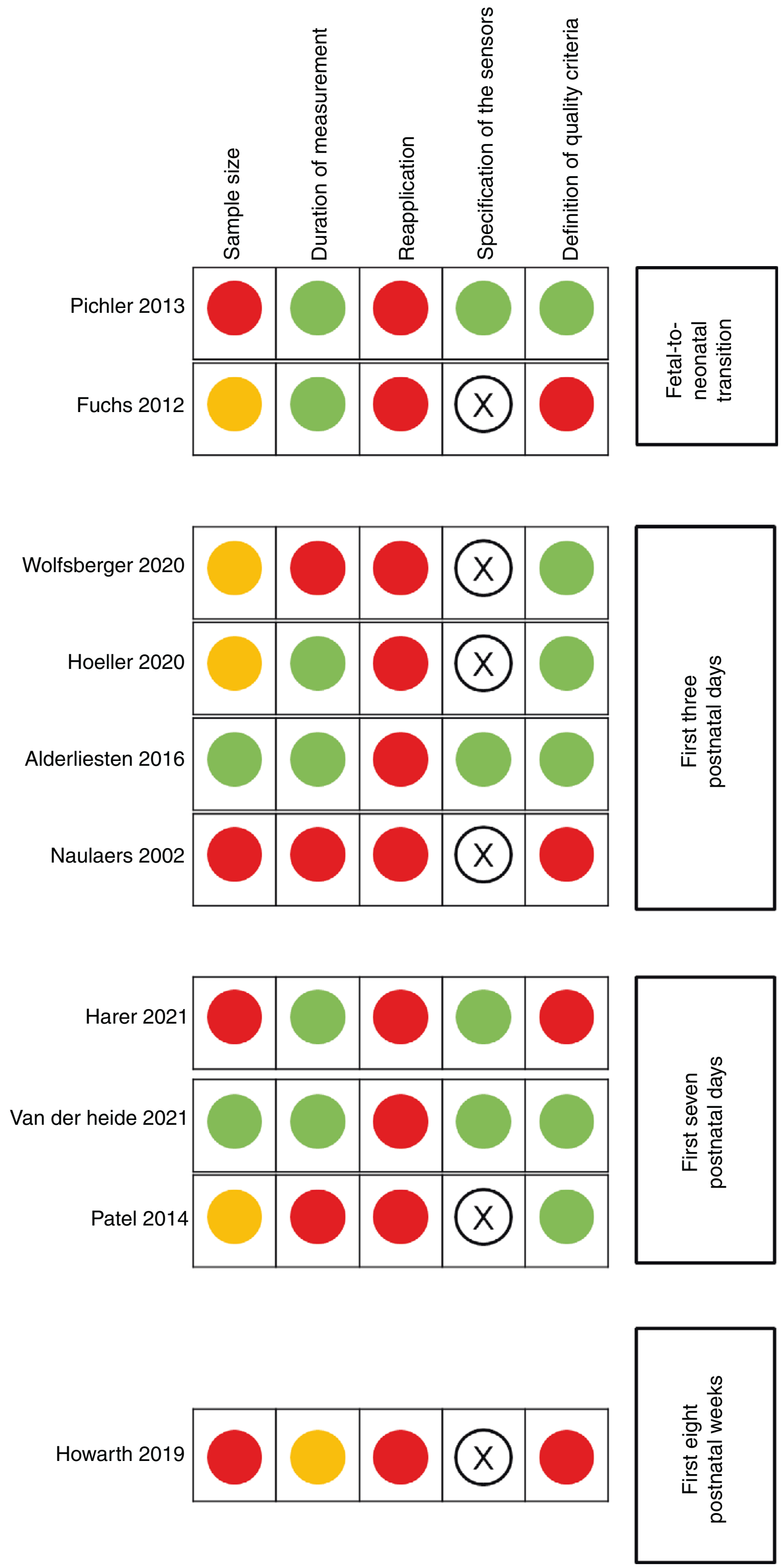

Fig. 3 Methodological quality criteria of studies in preterm infants. Sample size (red: $n = 10–50$, yellow: $n = 50–100$, green: $n > 100$); duration of the measurements (red: <1 h per measurement period, yellow: 1–8 h per measurement period, green: continuous measurement during study period); reapplication (red: no/not mentioned); specification of the used sensor (red: no, X: not applicable, green: yes); definition of quality criteria to detect and eliminate artifacts (red: not defined, yellow: sparely defined, green: reported in detail).

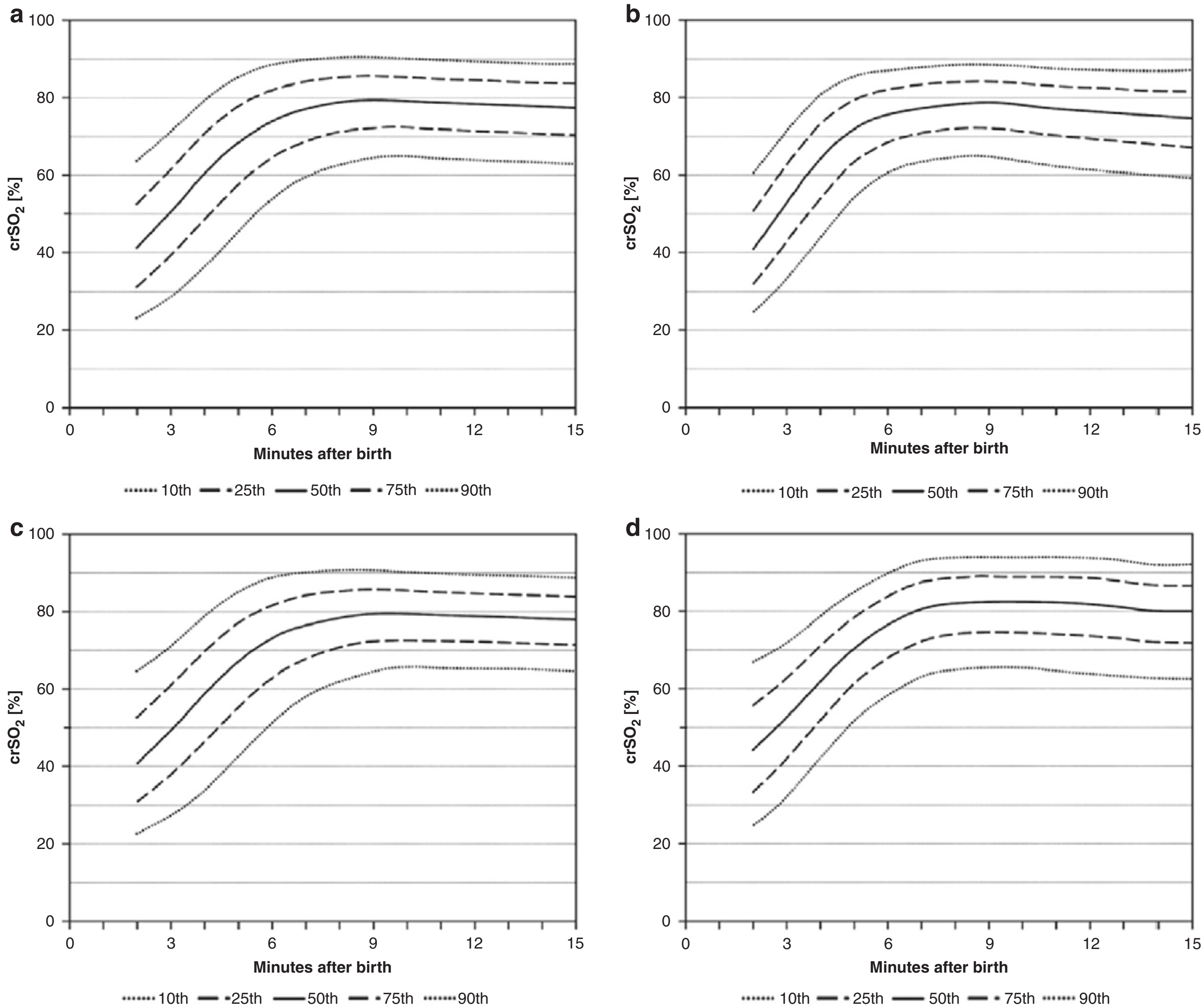

Fig. 4 The 10th, 25th, 50th, 75th, and 90th percentiles of cerebral regional oxygen saturation ($crSO_2$) in neonates requiring no medical support during the first 15 min after birth. **a** All neonates, **b** term neonates after vaginal delivery, **c** term neonates after cesarean delivery, **d** preterm neonates after cesarean delivery.[6]

birth.[23] Furthermore, the type of sensor utilized was not specified and no quality criteria were defined. Due to these limitations, the normal values of this study should be scrutinized before using them in a clinical approach.

In preterm neonates, three studies describing cerebral regional tissue oxygen saturation[8,12,19] and two studies describing muscle tissue oxygen saturation[11,12] are available. The strengths of the study by Alderliesten et al.[19] are the large sample size, the continuous measurement up to 72 h after birth, and that centile charts were generated for different gestational age groups (Fig. 5). The main limitation of the centile charts by Alderliesten et al. is that most of the neonates included had some medical support (e.g., non-invasive or invasive respiratory support, vasopressor medication), which might have influenced the cerebral regional tissue oxygen saturation.[19] The inclusion of preterm neonates with the need of medical support might result in a heterogeneous study group. However, generating centile charts in preterm neonates without any medical support in the first days after birth is unrealistic, especially in very low gestational age preterm neonates. Therefore, the use of centile charts generated in preterm neonates with medical support should be considered, but interpretation should include treatment protocols. Wolfsberger et al.[11] and Hoeller et al.[12] generated normal values for peripheral muscle tissue oxygen saturation in preterm infants < 37 weeks of gestation. Wolfsberger et al.[11] included a large sample size of preterm infants ($n = 100$). For peripheral muscle oxygenation and perfusion measurements, NIRS was used in combination with the venous occlusion method.[11] Preterm neonates were stratified into four time periods during the first day after birth according to their time point of measurement and matched for gestational age ±1 week.[11] Hoeller et al.[12] performed continuous, simultaneous cerebral and peripheral muscle tissue oxygen saturation measurements lasting 24 h (24–30 h after birth) in preterm neonates without signs of inflammation/infection and/or arterial hypotension.

First 7 postnatal days

Bernal et al.[24] published normal values of cerebral and renal regional tissue oxygen saturation in 26 term neonates. The main limitations of this study include a small sample size and normal values of renal tissue oxygen saturation ranging from 70 to 94% with a standard deviation of up to 12%, which suggests a high test–retest variability. Furthermore, there are some limitations of the NIRS measurement of renal tissue oxygen saturation. Pichler et al. investigated renal oxygen saturation in a neonatal piglet model by placing the NIRS sensor directly on the kidney and the

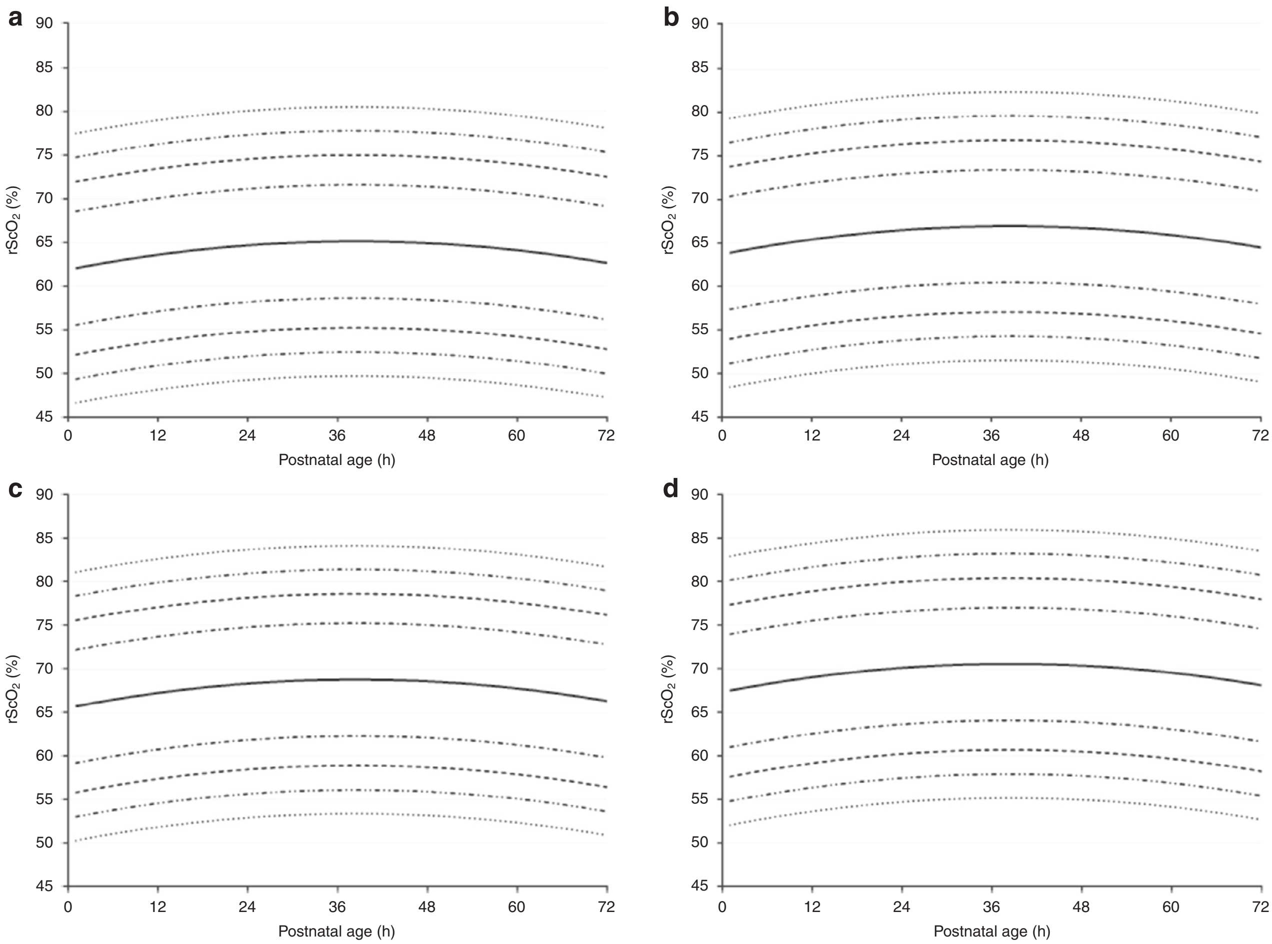

Fig. 5 Cerebral regional oxygen saturation (rScO_2) reference value curves within the first 3 days after birth for neonates. a 24–25 weeks gestational age, **b** 26–27 weeks gestational age, **c** 28–29 weeks gestational age, and **d** 30–31 weeks gestational age. The line patterns depict different percentiles: dotted lines indicate percentile (p) 2.3 and p97.7, dash–dot–dot–dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash–dot–dash lines indicate p20 and p80, and solid lines indicate p50.[19]

skin above.[30] This study demonstrated that, during hypoxia, transcutaneous measurement of renal tissue oxygen saturation using NIRS underestimates acute renal tissue desaturation.[30] Harer et al. generated renal tissue oxygen saturation normal values for preterm infants, demonstrating significant differences in renal tissue oxygen saturation between infants with and without acute kidney injury.[16] However, measurement was not performed continuously and the sample size was very small (no acute kidney injury $n = 32$ vs. acute kidney injury $n = 3$).

The two studies, describing normal values for abdominal regional tissue oxygen saturation in preterm neonates, included a fairly large sample size and provided normal values for the first week after birth.[9,10] Van der Heide et al.[9] generated normal values by calculating the mean abdominal regional tissue oxygen saturation from 2-h periods per day by using the INVOS 5100c device. Noteworthy, the association of abdominal regional tissue oxygen saturation and gestational age, postnatal age, and small for gestational age was calculated in a prediction model and presented in normal values for those different groups.[9] The measurements by Patel et al.[10] were performed continuously for 5 min every day by using the InSpectra650 device within the first week after birth. Although the number of neonates included seems adequate, the distribution of values was highly variable (mean 77% [SD 14%]; median 80% [range 25–99%]). These widespread values suggest that mesenteric NIRS monitoring has important limitations due to high test–retest variability and low reliability.[31]

First 8 postnatal weeks

There is only one study describing normal values for cerebral and abdominal NIRS measurement for the first 8 postnatal weeks including preterm neonates with a median gestational age of 26 3/7 weeks (23 0/7–29 6/7). Cerebral and abdominal NIRS measurement were performed simultaneously every week for 60 min.[13] However, the normal values are published only as an abstract at a conference meeting, therefore methodological details cannot be assessed.

Limitations

We were unable to perform a meta-analysis due to the differences in study population, study aim (centile charts or normal values), devices used, and neonates' age at assessment. However, this is the first systematic review that provides a detailed overview of the available literature of normative values and centile charts for regional tissue oxygen saturation measured with NIRS in neonates.

Clinical application of NIRS based on normal values and centiles in neonates

The introduction of any new measures or modalities requires a three-step validation process. First, the feasibility and reproducibility must be properly analyzed in healthy control population. Second, establishment of reference ranges with normal patterns or centiles curves are necessary. Finally, only after reference ranges are properly established for a specific group of individuals can the clinical focus shift to understand the thresholds and to assess the efficacy of patient management strategies in different disease and states be accomplished. For example, Baik et al.[32] observed that preterm neonates, who developed an intraventricular hemorrhage, had a cerebral tissue oxygen saturation below the 10th centile of the reference ranges published by Pichler et al.[6] during the first 15 min after birth. However, this does not necessarily imply causality. In addition, Binder-Heschl et al.[33] reported that 20% of the newborn infants who reached a SpO_2 target of ≥80% in min 5 after birth still had cerebral tissue oxygen saturation values below the 10th percentile[6] suggesting the presence of cerebral hypoxia. In a phase I/II trial (COSGOD), it has already been demonstrated that with NIRS monitoring (using the 10th centile of the published reference ranges as lower limit) and defined interventions it is possible to prevent cerebral hypoxia during immediate transition.[4] Currently, a phase III trial (COSGOD III) to investigate whether NIRS monitoring and the use of centile charts[6] in combination with defined interventions improves preterm infants' outcome is ongoing.[34] Furthermore, the SafeBoosC phase III trial,[35] which is ongoing, investigates the benefit and harms of protocolized treatment based on cerebral NIRS monitoring using the 10th centile of the reference ranges published by Alderliesten et al.[19] as lower limit in the first 72 h of life.

Using NIRS to monitor regional tissue oxygen saturation, different NIRS devices from different companies provide systematically different oxygenation values that warrants caution when interpreting reference ranges.[36] In addition, not only different devices from different companies but also different sensors for one device might provide different oxygenation values. It has been demonstrated that regional tissue oxygen saturation values differ with a range between 10 and 14% when measured with the INVOS 5100 device using the adult, the pediatric, or the neonatal sensor. Values are higher when using the pediatric and neonatal sensors compared to the adult sensor.[37,38] Hence, consideration must be given to the individual device and sensor used to determine reference ranges. It has been shown that these differences between devices/sensor are systematical and that the values between two instruments are linearly correlated. There are mathematical equations published to convert NIRS values between devices and sensors.[36,39] This has to be kept in mind when determining the normal ranges for a specific instrument from the mentioned studies.

The authors of the present systematic review recommend NIRS monitoring and the use of reference ranges in neonates only in addition to routine monitoring. Until more results from the ongoing trials (COSGOD III and SafeboosC III) are available,[34,35] the routine use of NIRS in the care of neonates to guide any interventions cannot be recommended. However, if these randomized trials prove that NIRS monitoring to guide interventions improve the outcome of the neonates the present review highlights that it is important to use the reference ranges and interpret trends based on data that match the NIRS device, sensor, gestational, and postnatal age. The present review on reference ranges helps, in addition, to interpret data obtained in sick neonates of already published studies and to plan future studies. Furthermore, centile charts should be preferred over normal values, as current published normal values often lack quality or adequate sample size and centile charts are more practicable in a clinical setting, especially during fetal-to-neonatal transition.

CONCLUSIONS

This systematic qualitative review comprehensively investigated the current reference ranges of regional tissue oxygenation determined by NIRS monitoring in term and preterm infants. We identified 19 studies that described centile charts or normal values over four unique time intervals in the early neonatal period whereby three studies were identified describing centile charts of cerebral regional tissue oxygen saturation in a good methodological quality. Two out of the three described cerebral regional tissue oxygen saturation during fetal-to-neonatal transition and one during the first 72 h after birth. Studies describing normal values for regional tissue oxygen saturation often lack quality or adequate sample size. Therefore, centile charts should be preferred over normal values. Clinically, NIRS monitoring should be used only in combination with the correct reference values matching the NIRS device, sensor, gestational age, and postnatal age to avoid overestimation/underestimation of regional tissue oxygen saturation. Once these pitfalls are considered, the present review enables the provider to understand and judge the oxygenation measured and to apply the correct NIRS reference values.

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AUTHOR CONTRIBUTIONS

All members of the European Special Interest Group "Near InfraRed Spectroscopy" are listed in the Appendix. All these members have substantially contributed to the conception and revision of the manuscript and approved the final version to be published.

FUNDING INFORMATION

Financial support of publication costs by the European Society for Paediatric Research (ESPR) is gratefully acknowledged.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not required.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-021-01786-y.

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