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REVIEW

Optimal Oxygen Saturation in Extremely Premature Neonates

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SUMMARY

So far, great efforts have been made to understand the demands of extremely premature neonates (EPNs; born before the 28th week of gestation) on postnatal care, including optimal oxygen saturation, that will allow them to survive without disability. A major yet unresolved problem is to find an “optimal range” of their oxygen saturation and to maintain it without drops or increases, i.e., without hypoxia or hyperoxia. The individual sections of this paper deal with the changes of SpO₂ (an estimate of SaO₂ measured by pulse oximetry) that occur before, during, and after premature labor, postnatal factors affecting SpO₂, and especially how to find an acceptable compromise in choosing the most effective and minimally harmful range of SpO₂ for EPNs’ with the careful FiO₂ adjustment and continually monitored SpO₂. At present, the two SpO₂ ranges, narrow (90-94%) vs. wider (88-94%), are most discussed. However, the question of how much oxygen is too much or little remains unanswered. There is even a view that there is no uniform optimal SpO₂ range for EPNs, and that each newborn has its own, individually specific range that changes due to its intrinsic and/or extrinsic factors.

Key words: prematurity, extremely premature neonate, oxygen therapy, oxygen saturation, target range of SpO₂.

Introduction

Extremely prematurity remains a global health problem. Despite an increasing amount of knowledge in neonatology and technological advances during last two decades, the extremely premature neonates (EPNs') (below 28 weeks' gestation) remain at high risk for death and disability with 30-50% mortality and, in survivors, at least 20-50% of morbidity (Glass et al. 2015).

The conclusions of five large clinical trials from 2010-2016, comparing the effectiveness and safety of the higher (91-95%) vs. lower (85-89%) oxygen saturation range in EPNs', supported the higher oxygen saturation range due to lower institutional mortality despite an increased incidence of retinopathy of prematurity (ROP). However, the question of what is the optimal oxygen saturation for EPNs' remains still open. Discussions on this topic are continuing with periodically changing intensity without a final consensus being reached.

This review provides a summary of the current findings and opinions on how to provide an effective and safe oxygen treatment in the EPNs'.

Brief history of oxygen therapy in premature infants

In 1940-50, the liberal administration of oxygen to the preterm newborn infants caused literally an epidemic of retrolental fibroplasia (RLF) (Terry 1942, Campbell 1951, Cross 1951), today called as retinopathy of prematurity (ROP). The restriction in oxygen administration in the 1960-70 has brought the reduction of incidence of retinal damage, but mortality due to hypoxia and the number of premature infants affected by hypoxia have risen again.

Searching for the optimal markers of the oxygenation and their values in preterm neonates, indicating the risk of hypoxemia or hyperoxemia continues with the same intensity to this day. In 2007, the American Academy of Pediatrics (AAP) proposed to maintain oxygen saturation measured by pulse oximetry (SpO₂) within the pragmatically derived range of 85-95%, and

partial pressure of oxygen in arterial blood (PaO_2) between 50-80 mmHg (American Academy of Pediatrics, American College of Obstetricians and Gynecologists 2007). The European guideline of 2007 recommended maintaining SpO_2 below 95%, but the lower limit was not defined (Sweet et al. 2007). The latest version of European guideline for the administration of oxygen in the premature neonates, even extremely premature, recommends maintaining SpO_2 between 90-94% (Sweet et al. 2017).

Factors related to oxygenation

The key factors of neonatal oxygenation are effective breathing (ie. central control of breathing and the lung maturity), ventilation/perfusion ratio, partial pressure of oxygen (PO_2), cardiac output (CO), hemoglobin (Hb) concentration, and homeostasis of internal environment.

Oxygen capacity is the maximum quantity of oxygen that can be bound to each gram of Hb (i.e., $1.34 \text{ ml} \times \text{Hb level in gram}$). The number derived from this equation indicates the total oxygen-carrying capacity of Hb in a particular neonate.

Oxygen saturation means the oxygen content expressed as a percentage of oxygen capacity. Oxygen saturation tells how much oxygen is carried only if the amount of Hb is known (Glickstein 2007). About 97% of oxygen is bound to hemoglobin while 3% is dissolved in the plasma.

The hemoglobin-oxygen dissociation curve shows the different ability of fetal Hb (HbF) and adult Hb (HbA) to bind oxygen (**fig. 1**). The curve for the fetal Hb (HbF) is said to be shifted to the left of the HbA curve, representing the greater affinity of HbF for oxygen at any given PO_2 . This results in less of an ability of HbF to release oxygen to the tissues. Factors that shift Hb dissociation curve to the right (and thereby increase oxygen delivery to tissues) include increased body temperature, PCO_2 , red cell 2, 3-diphosphoglycerate (2, 3-DPG) content in erythrocytes, and decreased pH (Glickstein 2007; Cummings and Polin 2016).

Relationship between oxygen saturation of arterial blood (SaO₂) and PaO₂: – SaO₂ means the oxygen saturation measured directly (invasively) in the arterial blood. The relationship between SaO₂ and PaO₂ is reasonably linear at SaO₂ values < 80%, but the slope of that relationship changes at SaO₂ levels > 80%, resulting in large changes in PaO₂ with small changes in SaO₂. This relationship is even more exaggerated in the presence of HbF with the HbO₂ dissociation curve shifted to the left. Given that SpO₂ (i.e. oxygen saturation measured by pulse oximetry) measurements become poor predictors of actual PaO₂, particularly when the infant is receiving supplemental oxygen, it is still necessary to monitor both SpO₂/SaO₂ and PaO₂, especially when SpO₂ reaches the high limit values (Saugstad 2016; Cummings and Polin 2016).

Monitoring of oxygen saturation

Current “bed-side” methods monitoring neonatal oxygenation are both invasive and noninvasive (based on transcutaneous technique of measurement).

Invasive monitoring of PaO₂ and SaO₂ is associated with repeated sampling of arterial blood. The length of such monitoring and frequency of blood sampling is determined by the newborn's clinical condition and availability of arterial access.

Noninvasive oxygen monitoring is based on two technologies, the transcutaneous PO₂ measurement and pulse oximetry.

Transcutaneous PO₂ measurement (PtcO₂) – the method uses a Clark-type sensor that is applied tightly to the skin. The sensor is heated to 43-44 °C to produce local hyperemia, which maximizes capillary blood flow under the sensor. Tissue oxygen then diffuses across the epidermis to the sensor membrane, where it is chemically reduced, producing a current proportional to the PaO₂. A 10 to 15 min. equilibration time after sensor application is needed before the readings become available. Under optimal steady-state conditions, correlation with PaO₂ is 0.90 to 0.95 (Richardson and Eichenwald 1998).

Pulse oximetry - it is the most commonly used method of measuring oxygen saturation (SpO_2). Pulse oximeter reading is a transcutaneous estimate of SaO_2 . This technology is based on the principle that oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) differently absorb red and near-red light. A microprocessor in pulse oximeters has an algorithm that uses ratio to determine the percentage of Hb bound to oxygen (SpO_2) (Chan et al. 2013). HbF has fairly similar absorbance pattern compared to HbA leading to similar functional SpO_2 measurements (Arikan et al. 1998). The standard manufacturers' claim of accuracy of detection of SaO_2 using the SpO_2 measured by pulse oximeters is $\pm 2-3\%$ over the range of 70–100% SpO_2 (Milner and Mathews 2012). All together this can mean up to 6%, which may be a problem when measuring too narrow range of SpO_2 (Nitzan et al. 2014, Lakshminrusimha et al. 2015).

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A non-invasive method of monitoring PaO_2 is transcutaneous oximetry ($tcPO_2$). The readings of $tcPO_2$ closely correlate with values in arterial blood. The disadvantage of this method is the need to frequently change the position of measuring electrode on the skin of the neonate (because of the high local warm-up temperature of $43^\circ C$) and calibrate it.

The pulse oximetry and SpO_2 measurement. The most commonly used non-invasive method is undoubtedly pulse oximetry measuring oxygen saturation of the fetus or neonate (FpO_2/SpO_2). This technology is based on a different absorption of infrared light by oxygenated or deoxygenated hemoglobin (HbO_2 , Hb). The concentration of oxygen saturation measured by pulse oximetry (SpO_2) and arterial blood sample (SaO_2) differs by $\pm 2\%$ (Nitzan et al. 2014). The accuracy of measurement stated by the manufacturer is within $\pm 3\%$. All

together this can mean up to 6%, which may be a problem when measuring too narrow range of SpO₂ (Nitzan et al. 2014, Lakshminrusimha et al. 2015).

The accuracy measurement with pulse oximetry can be negatively affected by a number of factors such as clinical instability of the immature neonate, variable position of the measuring probe ("preductal" position is recommended; eg right upper limb), interfering light of the same spectral wavelength (eg phototherapy), Hb derivatives, transfusion of erythrocytes increasing the percentage of HbA or artifacts caused by physical activity of the child (Lakshminrusimha et al. 2015, Cummings and Polin 2016).

Near-infrared spectroscopy (NIRS) is another frequently used noninvasive technology, measuring the tissue oxygenation of the brain and myocardium. NIRS exploits the relative transparency of biological tissue to near-infrared light (700-1000 nm), and the wavelength dependent absorption characteristics of Hb, which varies with oxygenation. By monitoring the intensity of light passing through the brain at two or more wavelengths, observed changes in attenuation can be converted into changes in cerebral concentration of oxyhemoglobin (HbO₂) and deoxyhemoglobin (Hb). Depending on the manufactures, the device is able measure the ratio of HbO₂ to total Hb as the tissue oxygenation index (TOI) or the regional cerebral oxygen saturation (rSO₂) (da Costa et al. 2015). Both, TOI and rSO₂, can be used to calculate the fractional tissue oxygen extraction, which by taking varying arterial oxygen saturation measurement into account directly represents the balance between cerebral oxygen supply and cerebral oxygen consumption (Naulaers et al. 2007).

Oxygen saturation during fetal-neonatal transformation

In utero, the fetus develops at markedly lower PaO₂ than after delivery. PaO₂ in utero is about 3.4 - 4.6 kPa (25-35 mmHg), while after delivery in term infant is between 10.6 -12.0 kPa (80 up to 90 mmHg) (Gao and Raj 2010). The placenta is the principal site of fetal blood gas exchange. Within the placenta, chorionic villi are wrapping with mixed arterial-venous

maternal blood with a PO₂ around 55 mmHg (7.3 kPa). The exchange of blood gases itself takes place during the flow of blood through the fetal intervillous space (Wu et al. 2016).

Because HbF has a higher affinity to oxygen and its extraction from the intervillous space of placenta, and saturation with oxygen at the same PO₂ is higher than that of HbA (Vento and Teramo 2013). The provision of an adequate amount of oxygen to the fetus shifts along gestation. Studies performed in human fetuses have shown that before the 12th week of gestation, the median value of intervillous PO₂ is around 18-20 mmHg (2.4-2.7 kPa) and then steeply raises to median of 60 mmHg (8 kPa) at 14-18 weeks, and thereafter again decreases slowly to 45 - 48 mmHg (6 - 6.4 kPa) at 36 weeks gestation (Kiserud 2005, Schneider 2011).

Birth, even extremely preterm, triggers profound respiratory, circulatory and metabolic changes. Along with increasing lung aeration the pulmonary vascular resistance decreases, right-to-left vascular shunting closes, pulmonary blood flow increases, and required ventilation/perfusion ratio is set. Concurrently, the blood from the right ventricle is redirected to the lungs where it is oxygenated. During the first 5-10 min after birth, PaO₂ increases from 40-50 mmHg (5.3-6.7 kPa) to 70-80 mmHg (9.3-10.6 kPa) (Gao and Raj 2010). At the same time, the SpO₂ values in the term newborn infants reach up 95-98%. For premature infants (mean gestational age of 33 weeks) SpO₂ will rise up from 60% to approximately 95% (**tab. 1**) (Dawson et al. 2010, Torres-Cuevas et al. 2017).

Preterm birth exposes the neonates, including EPNs', to a sudden transition from the oxygen poor to the oxygen rich environment. A sharp increase in oxygen saturation after birth and the immaturity of antioxidant systems (enzymatic and non-enzymatic) may contribute to an oxidative stress and production of reactive oxygen species (ROS) (Saugstad 1990, Saugstad 2001, Buonocore et al. 2002, and Escrig et al. 2008). Hitka et al found the highest content of hydrogen peroxide in exhaled breath condensates of ventilated very preterm neonates within the first hours of life (**fig. 2**) (Hitka et al. 2004). This may suggest an

association of oxidative stress with extremely preterm delivery as the major cause of severe immaturity of the neonate including his protective antioxidant mechanisms. The immaturity of the defense systems against ROS has two major reasons. First, the anti-oxidation enzymes are becoming operational during the late gestation. An increase in their activities is taking place at the same time as maturation of pulmonary surfactant production. Concurrently, non-enzymatic antioxidants cross the placenta in increased quantities. Therefore, induction of antioxidants in response to an oxidant challenge does not routinely occur in preterm infants born before 32nd weeks' gestation (Davis and Auten 2010).

Target range of SpO₂ in extremely premature neonates

Searching for target range of oxygen saturation defining normoxemia in premature infants has been taking place since the late 1940s. Methods assessing or estimating the oxygenation of EPNs', incl. pulse oximetry, described in the previous section, only partially extended our horizon of knowing the optimal target range of SaO₂/SpO₂ in these babies. Therefore the question of what concentration of oxygen is "optimal" to them remains unanswered (Cummings and Polin 2016, Askie et al. 2017).

Pretty recently, the five major international randomized studies (American SUPPORT, Canadian COT, and UK-Australian-New Zealand BOOST II) evaluating the effects of two pre-specified SpO₂ targets, i.e. low (85-89%) vs. high (91-95%), in EPNs' have been completed and their findings published (Carlo et al. 2010, Vaucher et al. 2012, Schmidt B et al. 2013, Stenson B et al. 2013, Tarnow-Mordi et al. 2016). These trials have been designed together so that EPNs' were randomly assigned to the one of two preselected SpO₂ ranges. Their primary outcome was a composite of death or disability at 18-24 months' corrected age, the secondary outcome included occurrence of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP). Death before discharge was a pre-specified secondary outcome only in the Boost II

studies (Manja et al. 2015, Cummings and Lakshminrusimha 2017). Data from over 5,000 tiniest neonates were collected and processed. Their analyses have shown that a higher target range SpO₂ (91-95%) was associated with lower mortality at the age of 36 weeks after conception (i.e. before discharge), but also with increased occurrence of severe ROP. Later meta-analysis didn't confirm the increased incidence of ROP as significant (Cummings and Lakshminrusimha 2017). On the other hand, the lower SpO₂ range (85-89%) was found to be associated with an increased mortality at 36 post-conception weeks' and more frequent NEC (necrotizing enterocolitis) (Stenson 2016).

The conclusions of studies attracted considerable attention and became the subjects of systematic analyses and reviews of the primary and secondary outcomes, along with the methods used, the level of evidence quality and the interpretation of findings (Sola et al. 2014, Lakshminrusimha et al. 2015, Manja et al. 2015, Cummings and Lakshminrusimha 2017, Askie et al. 2017). According to the reviewers view, the methods and interventions used in the reviewed trials had physiologic, technical, and implementation shortcomings that raised the questions about validity and applicability of acquired findings in the practice. The objections mainly concerned the age heterogeneity of neonates at enrollment, comorbidities between trials and change in oximeter algorithm midway through three trials (Lakshminrusimha et al. 2015, Manja et al. 2017).

Concerns raised mainly conclusions of SUPPORT II study on the causal link between restricted SpO₂ target range (85-89%) and increased institutional mortality (ie. before discharge home) or of increased incidence of severe ROP (\geq st. 3) in case of liberal SpO₂ range (90-95%) (Cummings and Lakshminrusimha 2017). Manja et al. pointed out that although EPNs' with a liberal (higher) oxygen target had significantly lower mortality before discharge, the quality of evidence for this finding is low (Manja et al. 2015). In addition, the last two systematic reviews have come to conclusions, that restrictive vs. liberal SpO₂ had no

significant effect on the primary composite outcome of death or major disability or on the major disability alone (Askie et al. 2017, Manja et al. 2017).

Interim concluding remarks

Currently, two concepts of the optimal SpO₂ target range - narrow (90-94%) and wider (88-94%) are being discussed. However, each carries the risk of either hypoxic or hyperoxic overlaps and is thus unacceptable (Sola et al. 2014; Sweet et al. 2017). **(tab. 2)** Manley et al. have recently reported that changing the SpO₂ target range from 88-92% to 91-95% led to a twofold increase in the incidence of severe ROP (Manley et al. 2016). In the report of 2016, American Academy of Pediatrics states that the ideal physiologic range of SpO₂ means a compromise between the negative consequences caused either by hyperoxemia or hypoxemia, but such ideal SpO₂ range for EPNs' remains unknown (Cummings and Polin 2016). In addition, any premature neonates, including those born extremely preterm, have probably individually different susceptibility or resilience to an impairment caused either by hypoxia or hyperoxia (Synnes and Miller 2015). Factors as corrected gestational age, postnatal age, growth, perinatal and neonatal comorbidity, extrinsic factors, all that may have impact on the severity and extent of hypoxic or oxidative impairment. It is unlikely that a single narrow SpO₂ range can be found that would be safe for all extremely premature neonates. Advances in avoiding the oxygen related impairments either for too little or too much of oxygen depends on the better understanding the pathophysiologic processes related organ injury, especially in the category of EPNs' (Cummings and Lakshminrusimha 2017).

Despite all efforts, considerable uncertainty persists about the desired target range of SpO₂ in EPNs'. Further studies should focus on studying newer methods of assessing oxygenation strategies to limit hypoxemia (< 85% SpO₂) and hyperoxemia (> 95% SpO₂). The latest reports on clinical experience with automated closed-loop of FiO₂ control of oxygen saturation look promising (van Zanten et al. 2017; van den Heuvel et al. 2018).

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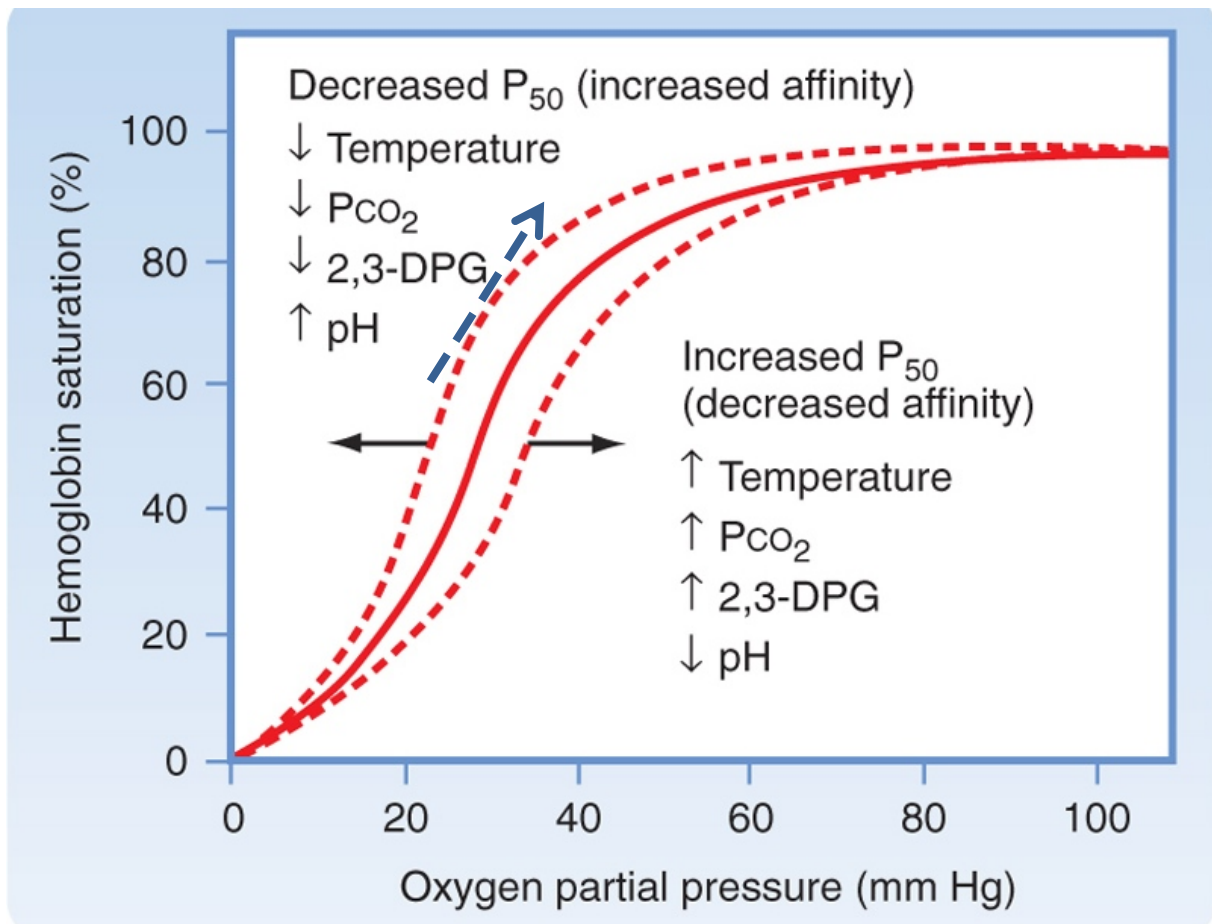


Fig. 1 Oxygen-hemoglobin dissociation curve and relationship between

SaO₂ and PaO₂ The curve for fetal hemoglobin is shifted to the left of the adult hemoglobin curve which means a higher affinity of fetal hemoglobin for oxygen and less ability to release oxygen to the tissues. SaO₂/PaO₂ relationship is reasonable linear at SaO₂ values up to 80% (see blue arrow), but at SaO₂ of 80% and above, the relationship becomes asymptotic and provides inaccurate estimate of PaO₂. Because the SaO₂ and SpO₂ values are not very different, SpO₂ measured by pulse oximetry will also be inaccurate for the PaO₂ estimate.

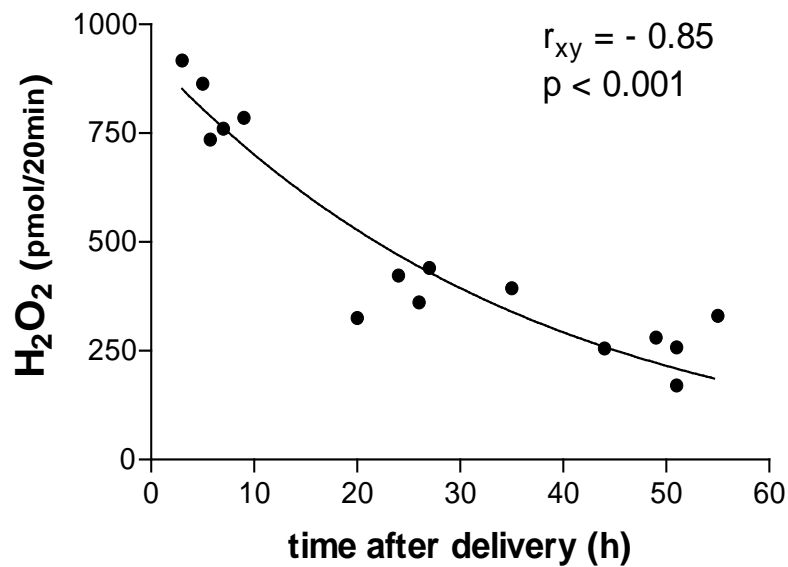


Fig. 2 Correlation between the times elapsed from delivery and H₂O₂ production in ventilated very premature neonates (Hitka et al. 2004).

Assessment of H₂O₂ concentration on expired breath condensates may provide information about immediate oxidative load in immature lungs. High production of H₂O₂ shortly after birth may reflect transition from fetal to neonatal oxygenation. Subsequent decrease of its values in expired breath condensates seems to be caused mainly by its reduced production.

Table 1 Spontaneous SpO₂ changes in term and preterm neonates after birth.

Term neonates: - time	SpO₂ (range):	b) Preterms: - time	SpO₂ (range):
1 min.	68% (60 - 77)	1. min.	62% (47 - 72)
2 min.	76% (65 - 84)	2. min.	68% (58 - 78)
3 min.	81% (71 - 90)	3. min.	76% (67 - 83)
4 min.	88% (78 - 94)	4. min.	81% (72 - 88)
5 min.	92% (83 - 96)	5. min.	86% (80 - 92)
10 min.	97% (94 - 98)	10. min.	94% (91 - 97)

(Data according to Kamlin et al. 2006, Dawson et al. 2010, Nuntnarumit et al. 2010)

Table 2 Some of frequently discussed recommendations to the oxygen therapy of very and extremely preterm newborns.

- 1) Stabilization after delivery:
 - Start with FiO_2 0.21 - 0.3;
 - Later – titrate FiO_2 according to the clinical status and actual $\text{SaO}_2/\text{SpO}_2$ values.
- 2) Frequently discussed target ranges of SpO_2 :
 - Higher and narrower target range of 91-94%;
 - Lower and wider target range 88-94% **[B2]**.
- 3) The wider range of SpO_2 - easier maintain SpO_2 values within desired range and prevent exceeding of alarm stings **[C2]**;
 - Setting alarm limits: - lower between 85-87%, upper between 94-96% **[D2]**.
- 4) Repeatedly exceeded SpO_2 target limits indicate examination of the PaO_2 and SaO_2 from arterial blood sample.
- 5) Hemoglobin (Hb) concentrations in extremely premature neonates with respiratory support and oxygen when considering transfusion of erythrocytes:
 - during the 1st week of birth: Hb 115 g/l (Hct 0.35);
 - until 2 weeks after delivery: Hb 110 g/l (Hct 0.30);
 - after the 2nd week of delivery: Hb 85 g/l (Hct 0.25) **[C2]**.

Grading according to the GRADE system (Guyatt HG et al., 2011)