

**OXYGEN USE IN INITIAL RESUSCITATION OF PRETERM INFANTS**

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*New European Resuscitation Guidelines from 2010 for initial resuscitation of term infants in the delivery room recommend use of room air instead of 100% oxygen. For preterm infants currently there is not enough data to conclude what is the most appropriate initial fraction of inspired oxygen needed for initial resuscitation. Delivery room must be equipped with oxygen blender and saturation monitor. Increasing oxygen concentration in resuscitation/stabilization of preterm infants should be titrated according to clinical and oxygen saturation responses.*

Descriptors: PRETERM INFANTS, INITIAL RESUSCITATION, OXYGEN

**Room air for resuscitation of term infants**

Use of supplemented oxygen used during neonatal resuscitation has been never validated in prospective controlled trials. A review of 6 randomized trials that compared use of room air (RA) and 100% oxygen reported that RA was associated with a significant lower mortality compared to 100% oxygen (13% vs 8%,  $P=0.0021$ ) (1). Despite the fact that results were similar to Cochrane review from 2005, the conclusion of the Cochrane review was still inconclusive saying there is not enough data to support either use of RA over 100% or vice versa. Results from different studies continuously revealed positive effects from RA:

- earlier initiation of spontaneous breathing;
- reduced mortality rate;
- no increase in neurodevelopment delay (2, 3).

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Based on current knowledge many neonatal units all over the world slowly shifted to use of RA or at least lowered starting fraction of oxygen in resuscitation of term infants during past ten years. Finally, in 2010 new European Resuscitation Guidelines have been published. The new recommendations say that in term infant's air should be used for resuscitation at birth; and only if, despite effective ventilation, oxygenation (ideally guided by oximetry) remains unacceptable, use of a higher concentration of oxygen should be considered (4).

**How much oxygen is enough for resuscitation/stabilization of preterm infants?**

The survival of extremely low birth weight (ELBW) infants has increased steadily over past years although mortality in the delivery room and during first 12 hours for ELBW is still high. Data from the Vermont Oxford Network compared to data from Neonatal intensive care unit (NICU) in Maternity Hospital Ljubljana are shown in Table 1, Table 2 and Figure 1.

In NICU Maternity Hospital Ljubljana delivery room (DR) oxygen is used only in 43% of infants with GA 22 to 29 wks whereas in VON database it is used almost in 91%. There is also much

higher percentage of infants without any medical intervention in DR (56% vs 6.7%). Contrary to opinion that very preterm infants need intensive resuscitation support after birth, the study from O'Donnell et al showed that the majority of extremely preterm infants cried (69%) and breathed (80%) without any medical intervention (5). Despite less aggressive management in DR the outcome measures in the NICU Maternity Hospital Ljubljana show more favorable results compared to VON database, especially in the much lower percentage of bronchopulmonary dysplasia (BPD).

**Golden hour-oxygen effect**

Intrauterine  $\text{PaO}_2$  levels in the fetus are in the 15-30 mm Hg (2-4 kPa) range resulting in fetal  $\text{SpO}_2$  levels of 45% to 55%. After delivery these levels will rise to 50-80 mmHg (6.7-10.7 kPa) (6). During resuscitation with 100% oxygen, the  $\text{SpO}_2$  may increase to >80 mmHg (>10.7 kPa) within 5 minutes of birth in some of these infants (7, 8). Many morbid conditions associated with extreme immaturity are aggravated by an excess of free-radicals occurring in infants who are intrinsically deficient in enzymatic antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase (9-11). Low plasma antioxidant activity at birth in premature infants was

Table 1  
Early deaths of infants with GA 22 to 29 wks; comparison between VON database and NICU Maternity Hospital Ljubljana

Tablica 1.  
Rana smrtnost dojenčadi s GD 22 do 29 tj.; usporedba između VON baze podataka i NIJ u rodilištu Ljubljana.

	died in DR smrtnost u rađaonici (%)	died within 12 hours smrtnost u roku od 12 sati (%)	early deaths rana smrtnost (%)
VON 2008	5.0	2.4	7.4
NICU Maternity Hospital Ljubljana 2008 NIJ u rodilištu Ljubljana 2008	4.9	2.1	7.0
VON 2009	5.0	2.4	7.4
NICU Maternity Hospital Ljubljana 2009 NIJ u rodilištu Ljubljana 2009	6.0	0	6.0

an independent risk factor for mortality (12). Further more, in preterm animals it was established that they are unable to upregulate deficient antioxidants (13). During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. BPD and neurological impairment are two major long term morbidities in ELBW. Pulmonary oxygen toxicity with enhanced inflammatory cytokine response to oxygen is believed to be a major contributor to the development of BPD (14-16). The brain is also adversely affected by reoxygenation injury, and such conditions may also help explain the underlying pathogenesis of periventricu-

lar leukomalacia (17). Mickel et al showed that reoxygenation with high oxygen concentrations after global brain ischemia caused increased lipid peroxidation and mortality in Mongolian gerbils (18). There are new preliminary data that also suggest that higher SpO<sub>2</sub> in the first four hours after birth in VLBW infants may be associated with lower impulse control and attention skills in the elementary school age period (19).

Saturation levels during first ten minutes of life in term and preterm infants

Healthy neonates are poorly saturated immediately after birth. In the study

from Altuncu et al median SpO<sub>2</sub> values in the first, fifth and tenth minutes were 71, 92, and 98% in vaginal deliveries and 70, 79, and 96% in caesarean deliveries, respectively (20). Dawson et al have recently reviewed saturation measurement during first 10 minutes of life from 2 centers for 160 preterm infants and 306 term infants (Figure 2, Figure 3 and Figure 4). The study documents 3<sup>rd</sup> to 97<sup>th</sup> percentile changes in preductal SpO<sub>2</sub> after birth for term and preterm infants with no medical interventions. These findings can be used to monitor changes in SpO<sub>2</sub> and to titrate oxygen treatment in the DR (21).

Is room air sufficient for resuscitation of ELBW infants?

The first prospective dual center randomized trial was performed by Wang et al (22). Newborns below 32 weeks of gestation were randomized to initiation of resuscitation with RA or 100% oxygen. Target saturations were 75% at 3 minutes and 85% at 5 minutes of life. When target SpO<sub>2</sub> was not achieved, inspiratory fraction of oxygen (FiO<sub>2</sub>) was increased in steps of 0.25. When severe bradycardia was present, FiO<sub>2</sub> was immediately switched to 1.0. Because every patient in the RA group required oxygen by 3 minutes of age and at 5 minutes SpO<sub>2</sub> were significantly lower (<80%) in RA group, authors concluded that resuscitation with RA is not recommended for very preterm infants.

In an observational study Dawson et al measured SpO<sub>2</sub> and heart rate in two groups of infants with GA <30 wks after

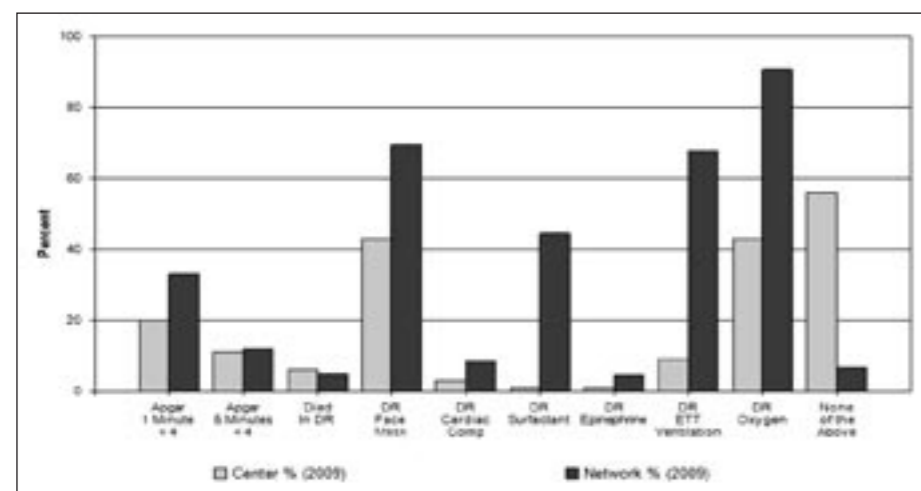


Figure 1  
Initial resuscitation; infants GA 22 to 29 wks; comparison between VON database and NICU Maternity Hospital Ljubljana for 2009 (bright bars NICU Maternity hospital Ljubljana, dark bars VON database)

Slika 1.  
Početno oživljavanje; novorođenčad GD 22 do 29 tj.; usporedba između VON baze podataka i NIJ u rodilištu Ljubljana za 2009. (svijetli stupci NIJ Rodilišta u Ljubljani, tamni stupci VON baza podataka)

Table 2  
Mortality, mortality and major morbidity, BPD in infants GA 22 to 29 wks; comparison between VON database and NICU Maternity Hospital Ljubljana

Tablica 2.  
Smrtnost, smrtnost i morbiditet, BPD u novorođenčadi GD 22 do 29 tj.; usporedba između VON baze podataka i NIJ Rodilišta Ljubljana

	Mortality smrtnost (%)	mortality or morbidity smrtnost i morbiditet (%)	BPD (%)
VON database 2008 VON baza podataka 2008	21.0	62.7	35.3
NICU Maternity Hospital Ljubljana 2008 NIJ u rodilištu Ljubljana 2008	19.6	44.1	12.3
VON database 2009 VON baza podataka 2009	20.7	62.1	35.3
NICU Maternity Hospital Ljubljana 2009 NIJ u rodilištu Ljubljana 2009	14.1	40.4	16.3

10 minutes of resuscitation either with room air or 100% oxygen. Results were similar to Wang's study. Majority of very preterm infants received supplemental oxygen if air was used for the initial resuscitation. Of the infants resuscitated with 100% oxygen, 80% had SpO<sub>2</sub> ≥95% during the first 10 min. The heart rate (HR) changes in the two groups were very similar (23).

The ROAR study (RA versus oxygen administration during resuscitation of preterm infants) combined 3 different

strategies. One group was resuscitated with 100% oxygen, and two other groups received 100% oxygen or RA as initial gas, which was then titrated according to SpO<sub>2</sub>. The aim of the study was to achieve SpO<sub>2</sub> between 85% and 92% by the end of resuscitation. The strategy of starting the resuscitation with 100% oxygen followed by titration of FiO<sub>2</sub> was the most effective at maintaining SpO<sub>2</sub> in the target range (24).

In a prospective, randomized trial Escrig et al randomly assigned infants

below 28 weeks of gestation who required active resuscitation to the low-oxygen group (FiO<sub>2</sub> 30%) or the high-oxygen group (FiO<sub>2</sub> 90%) (25). Oxygen delivery was titrated regarding saturation value and heart rate. The fraction of inspired oxygen in the low-oxygen group was increased stepwise to 45% and that in the high-oxygen group was reduced to 45% to reach a stable SpO<sub>2</sub> of approximately 85% at 5 to 7 minutes in both groups. No differences in mortality rates in the early neonatal period were detected. They concluded that resuscitation can be safely initiated for extremely low gestational age neonates with low FiO<sub>2</sub> (approximately 30%), which then should be adjusted to the infant's needs, reducing the oxygen load to the neonate.

Vento et al (26) in prospective, randomized study in infants of 24 to 28 wks of gestation compared 30% to 90% oxygen at the start of resuscitation and a targeted SpO<sub>2</sub> strategy during resuscitation. The 30% group had shorter duration of oxygen treatment (6 days vs. 22 days; p<0.01), mechanical ventilation (13 days vs. 27 days; p<0.01), and had a lower incidence of BPD at discharge (15.4% vs. 31.7%; p<0.05). Markers of oxidative stress in blood and urine were significantly increased in the 90% oxygen group. They also established that concentrations of isofurans, ortho-tyrosine and 8-hydroxy-2'-deoxy-guanosine (on day 7) significantly correlated with development of BPD.

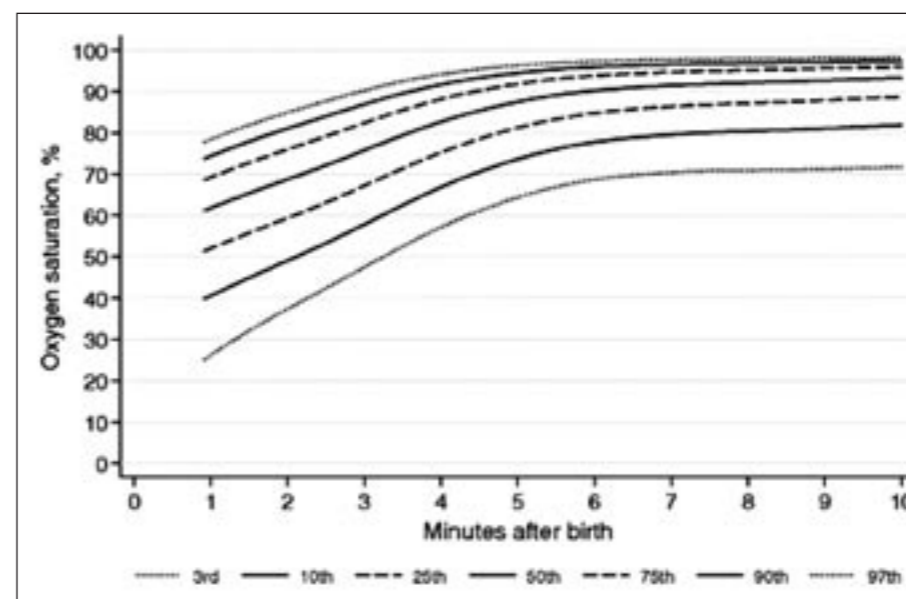


Figure 2  
Oxygen saturation in infants with GA <32 wks with no medical intervention in the first 10 minutes after birth by Dawson et al (21)

Slika 2.  
Saturacija kisikom novorođenčeta GD <32 tj. bez medicinske intervencije u prvih 10 minuta nakon porođaja po Dawson i sur. (21)

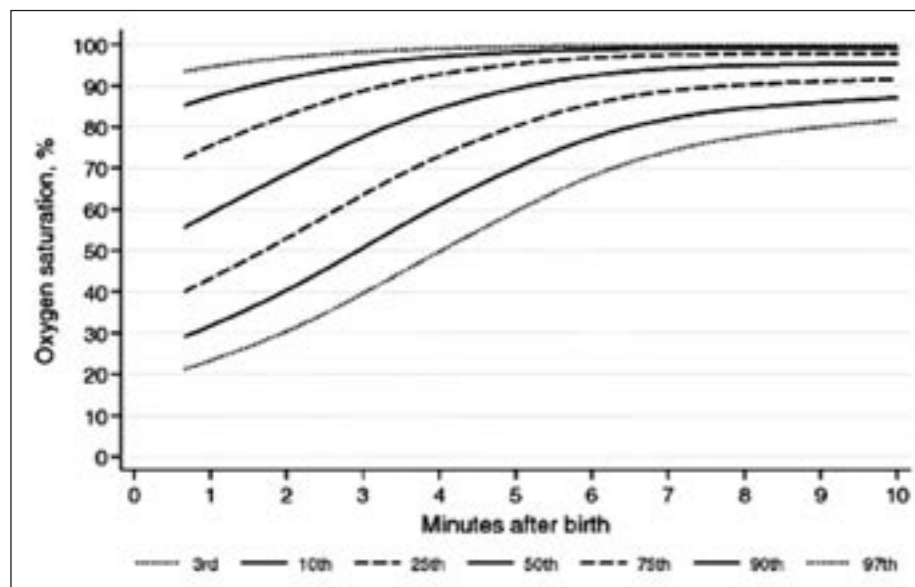


Figure 3  
Oxygen saturation in infants with GA at 32 to 36 wks with no medical intervention in the first 10 minutes after birth by Dawson et al (21)

Slika 3.  
Saturacija kisikom novorođenčeta GD od 32 do 36 tj. bez medicinske intervencije u prvih 10 minuta nakon porođaja po Dawson i sur. (21)

Preliminary conclusions based on current knowledge about oxygen use in resuscitation/stabilization of preterm infants

Conclusions drawn from the published studies about the use of oxygen in resuscitation of preterm infants are (27):

- Preterm infants need some oxygen for the resuscitation/stabilization immediately after birth.
- Exposure to excessive amount of oxygen increases oxidative stress.
- Increased oxygen concentration should be titrated according to clinical and SpO<sub>2</sub> responses.
- In newborns with severe circulatory arrest, the heart rate response to the first ventilations even before obtaining a reliable reading from pulse oximeter should guide oxygen use. When the heart rate does not increase despite adequate ventilation, oxygen should be rapidly increased to attain a return of spontaneous circulation.
- Extremely low gestational age newborns should be monitored for preductal SpO<sub>2</sub> and heart rate immediately

after birth when possible; delivery room must be equipped with oxygen blender and saturation monitor. Reliable reading of saturation obtained simultaneously in neonatal critical si-

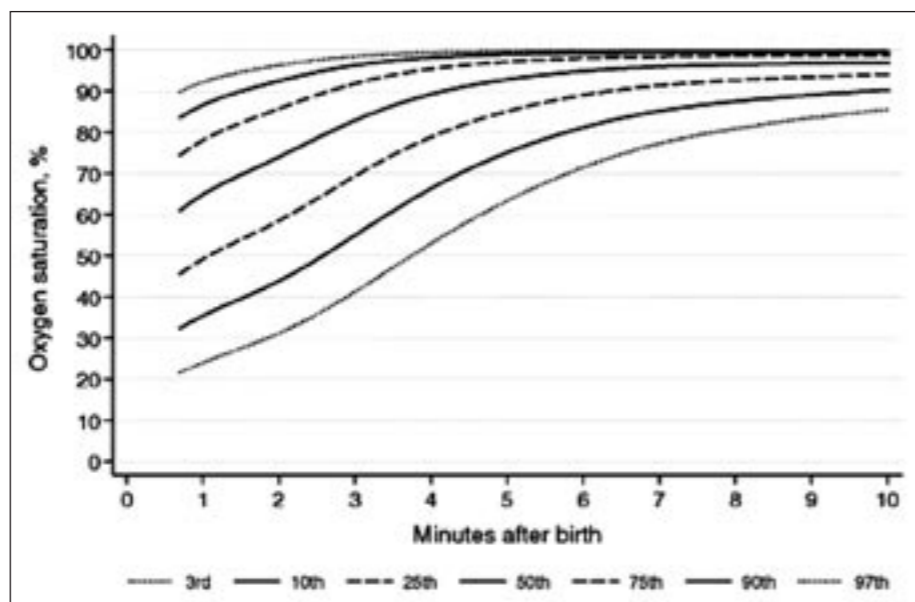


Figure 4  
Oxygen saturation in infants with GA ≥37 wks with no medical intervention in the first 10 minutes after birth by Dawson et al (21)

Slika 4.  
Saturacija kisikom novorođenčeta GD ≥37 tj. bez medicinske intervencije u prvih 10 minuta nakon porođaja po Dawson i sur. (21)

tuations differs by the type of the pulse oximeter used, being significantly faster with Masimo Signal Extraction Technology. This may permit better adjustments of inspired oxygen aiding in the prevention of damage caused by unnecessary exposure to high or low oxygen (28).

Large, randomized, blinded, prospective studies to establish the most appropriate initial fraction of inspired oxygen

Before further recommendations about the most appropriate initial fraction of inspired oxygen, large, randomized, blinded, prospective trials are needed. Currently two such trials are being planned (29):

- US based (will involve also centers in Canada and Europe, including Neonatal Intensive Care Unit, Maternity Hospital Ljubljana).
- Australia based trial.

The plan for both trials is to enroll over 1200 infants. In US based trial, infants from 23 to 29 wks will be randomized either to low oxygen group (21% oxygen) or high oxygen group (90% ox-

xygen). The FiO<sub>2</sub> will be increased or decreased in 0.1 increments to maintain the SpO<sub>2</sub> level between 65% and 85% for the first 10 minutes. Both trials include neurodevelopmental follow up at 2 years.

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*Sažetak*

PRIMJENA KISIKA U POČETNOM OŽIVLJAVANJU NEDONOŠČADI

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*Nove Evropske smjernice za oživljavanje iz 2010. preporučuju za početno oživljavanje donošene novorođenčadi u rađaonici primjenu sobnog zraka umjesto 100% kisika. Za nedonoščad trenutno nema dovoljno podataka iz kojih se može zaključiti koji postotak kisika upotrijebiti za početno oživljavanje. Rađaonica mora biti opremljena sa dovodom zraka različite zasićenosti kisikom i monitorom za praćenje saturacije. Povećavanje koncentracije kisika tijekom oživljavanja nedonoščadi treba biti u skladu s koncentracijom plinova u krvi.*

Deskriptori: NEDONOŠČAD, POČETNO OŽIVLJAVANJE, KISIK