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Review Article

Oxygen Therapy in Neonate: A Vital Issue

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Introduction

Oxygen is the most common drug used in neonatology worldwide[1]. Inappropriate supplementation of oxygen may not decrease hypoxia or may lead to development of hyperoxia. Hypoxia may lead to pulmonary vasoconstriction, pulmonary hypertension, neurological and other organ damage[2]. This condition may be associated with lethargy, cyanosis, hypothermia, fixed heart rate of 120/min or bradycardia, metabolic acidosis or unresponsiveness to therapy[3]. Hyperoxia, on the other hand, produces complex physical and physiological stress[4]. It produces free radical mediated cellular damage through lipid peroxidation, inactivation of enzymes, damage of DNA and structural protein. It is believed that a number of diseases in the newborn may occur as consequences of oxygen free radicals e.g. retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis and patent ductus arteriosus etc[3].

Oxygen therapy needs urgent response from clinician through proper monitoring. The primary aim of monitoring of oxygen is to reduce hypoxic and hyperoxic episodes and to decrease the variability in an infant's oxygen levels by enabling close continuous monitoring[5]. There are many monitoring systems of oxygen status in neonates. Many of our clinicians are not acquainted of normal oxygen level of our neonates. There is scarcity of knowledge among our physicians regarding monitoring of oxygen status. Many studies on oxygen therapy are conducted in different parts of the globe. But studies in neonatology in our country are very lacking. This review is written to orient our clinicians regarding some fundamental aspects of oxygen therapy in neonates so that inappropriate oxygen related morbidity and mortality could be minimized.

Oxygen levels in newborn infants:

Oxygen levels in newborn infants are studied by different researchers:

On 115 newborn infants at 5 minutes of age, the observed median SpO_2 values were 87% for infants delivered vaginally and 81% for those delivered through cesarean section. The median SpO_2 did not reach 90% until 8 minutes of age in either group[6]. In another study, the researchers observed median SpO_2 at 1 minute was 63%. There was gradual rise in SpO_2 with time, with a median SpO_2 at 5 minutes of 90%[7]. Another group of researchers showed that the best fixed lower and upper limits for SpO_2 was 91% (sensitivity of 0.72 and specificity of 0.56) and 96% (sensitivity of 0.80 and specificity of 0.59)[8].

Arterial oxygen tension (PaO_2) values in infants <29 weeks of gestation was studied. The 95% CI of PaO_2 for the SpO_2 range 85-95% was 3.8 to 8.9 kPa. The mean (95% CI) PaO_2 at a saturation of 85% was 5.3 (3.8 to 6.8) kPa and at a saturation of 95% it was 7.2 (5.5 to 8.9) kPa. The researchers concluded that saturations within the range 85-95% largely exclude hyperoxia in preterm infants <29 weeks' gestation but permit PaO_2 values far lower than those recommended in traditional guidelines[9]. Oxygen level (SpO_2) observed in Bangladeshi neonates were 95% in 1st and 2nd weeks, 94% in 3rd and 92% in 4th week of postnatal age. The normal SpO_2 value in terms of normal PaO_2 value observed in those neonates ranged from 87% (sensitivity=71%, specificity=100%) to 94% (sensitivity=94%, specificity=73%)[10].

Goal and principles of oxygen therapy:

The goals of oxygen therapy in neonate are (i) to maintain adequate partial pressure of oxygen in arterial blood (PaO_2), (ii) to minimize the cardiac work and (iii) to minimize the work of breathing[11]. It is important to realize that optimal oxygenation will result in different PaO_2 goals for different sick neonates.

The main principle of oxygen therapy is to provide oxygen in such quantities that it will be neither 'high' nor 'low' for neonatal health. Oxygen should be administered only when indicated, given in the lowest ambient concentration and should be stopped as soon as its use is considered unnecessary[3]. Most commonly, premature infants in respiratory failure should have PaO_2 values between 50-80 mmHg[11]. A PaO_2 values of <40 mmHg and >80 mmHg is also regarded as 'low' and 'high' PaO_2 values by neonatologists[12]. Maintenance of partial pressure of oxygen within such range minimizes the chances of

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Table - A

Effects of oxygen on neonate at different saturations

References	Study group	SpO_2 ranges compared (%)	Survival rate (%)	Incidence ch. lung disease (%)	Incidence of retinopathy of prematurity (%)
Tin et al, 2001	<27 week	Low=80- 90	53%	18	
		High=94- 98	52%	46	
				p<0.01	
Sun, 2002	<1500 g	Low < 95	83	27	10
		High > 95	76	53	29
				p<0.0001	p<0.0001

blindness caused by retinopathy[11]. In very low birth weight newborns, when treating with oxygen, a PaO_2 of 41 mmHg may be enough to saturate 90% of hemoglobin at a physiological pH[13].

Strict management of oxygen delivery and monitoring to minimize episodes of hyperoxia and hypoxia was associated with decreased incidences of retinopathy of prematurity (ROP) over a period of 5 years from 12.5% in 1997 to 2.5% in 2001[14]. Full-term neonates with diaphragmatic hernia or persistent pulmonary hypertension may require more PaO_2 values to maintain stability and avoid worsening pulmonary hypertension[11]. The objective of oxygen therapy in infant with bronchopulmonary dysplesia is to avoid use of high inspired oxygen concentrations while maintaining adequate oxygenation[15]. Study showed that the incidence of chronic lung disease and retinopathy of prematurity was significantly increased when oxygen of higher concentrations was administered (Table-A)[5].

A PaO_2 value of 40-80 mmHg corresponds to SpO_2 values of 85-93% in majority of cases[12]. Generally, SpO_2 is maintained at 85% to 95% (85% - 92% if <29 weeks gestation) range[16]. The alternate option regarding oxygen therapy is that the arterial oxygen saturation should be maintained between 90-95% for acute conditions and 85-90% for chronic situations[3].

Indications and Methods of Oxygen Therapy:

Followings are important indications of oxygen therapy[3]:

(i) *Perinatal asphyxia*. (ii) *Cyanosis* (excluding congenital cyanotic heart disease without cardiac failure and methemoglobinemia). (iii) *Respiratory distress*-due to hyaline membrane disease, pneumonia, cardiac failure and congenital malformations. Oxygen therapy is indicated if respiratory distress is worsening or if any feature of hypoxia is evident or if PaO_2 is <40 mmHg or SpO_2 <85%. (iv) *Hypothermia.* (v) *Recurrent apneic spell. (vi) Pneumothorax or pneumomediastinum.* Inhalation of 100% oxygen would facilitate earlier resorption of air but drainage of air is life saving in a case of tension pneumothorax[3].

There are several different methods of 'non-invasive' oxygen administration namely, administration through *nasal prongs, nasal catheter, nasopharyngeal catheter, oxygen hood (head box), face mask and holding oxygen source* close to the infant's face[17]. Oxygen may also be given through *endotracheal tube* connecting with self inflating bag, continuous positive airway pressure (CPAP) or ventilator system[18]. Oxygen administration through cannula and nasopharyngeal catheters may be regarded as 'semi-invasive' methods and need less oxygen and economic. In case of nasal catheter, it is passed equal to the distance from the side of nostril to the inner margin of the eyebrow and nasopharyngeal catheter is inserted to the distance from the side of the nose to the front of the ear[17]. Through nasal cannula oxygen delivery can be controlled by flowmeters to as little as 0.025L/min. Flow rate of >1L/min may impart distending airway pressure through this technique. When 100% oxygen with flow rate of 0.5 L/min is supplied through a cannula, it delivers ~44% oxygen. Around 66% oxygen is delivered if flow rate is 1L/min through a cannula[18]. Giving oxygen by head box needs relatively high flows to achieve adequate concentrations of oxygen[17]. The main complications of methods of oxygen administrations are hypercarbia with head box and face mask, dislodgement with nasal cannula and obstruction of the catheter or upper airway, as well as gastric distension, with nasopharyngeal catheters.[17]

Monitoring of oxygen:

In emergency situation sufficient oxygen should be administered to abolish cyanosis or when oxygen therapy is otherwise indicated. It is useful to monitor ambient oxygen concentration by 'oxygen analyzer' in order to protect infant against oxygen toxicity. It helps in regulating the flow rate of oxygen so that desired concentration of oxygen can be delivered to infant[3]. However, monitoring of oxygen directly on newborn infant is very important and should be initiated as soon as possible.

Objectives of oxygen monitoring:

The objectives of oxygen monitoring is to prevent oxygen mediated complications of hypoxia or hyperoxia notably reduction of injury to lungs, immature retina and other tissues**.**

In the long run the purpose of oxygen monitoring is to detect degree of hypoxia, which is likely to cause acidosis or tissue damage and levels of hyperoxia, which may risk predominantly retinopathy of prematurity[19].

Monitoring systems:

Cyanosis may be a guide for oxygen status in body, but it is very much subjective and evident only when saturation is markedly low. Again, plethoric and polycythemic patient may appear cyanosed despite adequate arterial oxygen tension[20]. The followings are important monitoring systems of oxygen therapy:

1. Arterial blood gas (ABG) analysis:

Blood gas measurement provides the clinician with information essential to patient assessment, therapeutic decision-making and prognostication. Blood gas measurements are as important as for ill newborn infants as for other critically ill patients[11].

***Usual values:** The normal values of arterial blood gases are very dependent on many factors including gestational age and postnatal age of infants[11].However, a value of 50-80 mmHg is considered as target range of partial pressure of oxygen of arterial blood (Pao_2) for newborn infants[16].

***Sampling sites:** This require arterial puncture or and indwelling arterial catheter. Access via the umbilical artery or peripherally is now considered route[18]. Radial or posterior tibial arteries are commonly used, but ulner, dorsalis pedis and axillary arteries are alternatives[21].

***Complications:** Complications related to radial artery puncture include: (i) hematoma formation (ii) arterial spasm, thrombosis and embolism (iii) infection and (iv) inaccuracy of blood gas results[18].

***Merits and demerits:** Direct blood gas sampling from arterial lines to measure partial pressure of oxygen in arterial blood (PaO_2) is considered to be the gold standard for accuracy. This method, however, only provides intermittent oxygen monitoring. It is invasive, can lead to significant blood loss and erroneous results may be found if sampling is improper. New micro method ('two-needle technique') of arterial blood gas sampling may be preferable to commonly used 'drip technique' specially for low birth weight infants in whom minimization of blood loss is essential[22]. Moreover, such facility is very limited in countries like ours.

2. Continuous blood gas monitoring:

Continuous blood gas monitoring through an indwelling catheter has been advocated to provide rapid, real-time data and reduce the volume of blood required for repeated blood gas measurements.

Recent technology has been utilized for fiber optic systems optical sensors inserted into vascular catheters already in place. These devices have been used for circuit monitoring during neonatal extracorporeal membrane oxygenation (ECMO) and for monitoring of premature infants through umbilical artery catheters. Reported correlation with measured PaO_2 values is good in some studies but bias and precision of measurements deteriorate for PaO_2 values above 70 mm Hg. The sensor also can not be threaded into some brand of umbilical catheters smaller than 5 Fr.[16].

3. Capillary blood gas determination:

This technique requires extensive worming of the extremity, free-flowing puncture, and strictly anaerobic condition. Under such conditions, capillary sample may be useful for determination of pH and PcO_2. Proper collection techniques are often difficult to guarantee in technical setting; however, capillary sample should not be used for determination of PaO_2[16].

4. Pulse-oximetry (SpO_2):

It is very difficult to guess the state of a patient's arterial oxygenation subjectively. The introduction in the early eighties of pulse-oximetry allows reasonably accurate

objective assessment of P_aO_2[23]. Its routine availability will help to pick up any significant change in oxygen saturation in newborn infants[24]. Study has shown that using pulse-oximetry as a routine 'fifth vital sign' resulted in important changes in the treatment of a proportion of patient[25]. Control of oxygenation is achieved by maintaining saturation within a target range, usually by setting alarm limits[9].

(i) Principles of working:

Oximeter makes use of the fact that oxyhaemoglobin and deoxyhaemoglobin absorb light at the red end of the spectrum differently; deoxyhaemoglobin absorbs more red than infrared and oxyhaemoglobin more infrared than red[26]. The wavelengths of red and infrared light are 660 nm and 940 nm respectively[27].

The oximeter probe consists of a 'light emitter' and a 'light sensor', which are aligned on opposite sides of a narrow part of body, such as palm or forefoot. The 'emitter' sends equal intensities of red and infrared light into the tissue. The 'sensor' detects the ratio of red to infrared that emerges. From this information the proportion of oxyhaemoglobin to deoxyhaemoglobin-that is, the percentage saturation of haemoglobin with oxygen is calculated and displayed[26]. As oximeter measures the saturation of arterial blood rather than capillary or venous blood, the instrument is programmed to look only at pulsatile increases in oxyhaemoglobin concentration-hence the term 'pulse' oximetry[26]. The pulsatile signals are due to variability of arterial cross-sectional area and change in axis of erythrocytes with each cardiac cycle[23]. When light is passed through tissue some of the light is absorbed by each constituent of the tissue, but the only variable light absorption is by arterial blood[28].

(ii) Advantage and disadvantage of pulse-oximetry:

It is non-invasive, less complex, does not require calibration and provides continuous measurement of hemoglobin-oxygen saturation (Spo_2)[16]. Response time of this instrument is fast[29] and accuracy is high (±3%)[16]. The main disadvantage of pulse oximeter lies on its limitations. The '*safe limitation*' is that when the machine is not indicating the correct value of SpO_2 and the user is warned that the value may be incorrect. '*Dangerous limitation'* is that when the machine appears to operating satisfactorily but actually operating wrong value of SpO_2[23]. Complications associated with use of pulse oximetry have been reported. These include pressure erosion, skin necrosis, digital sensory loss and even burn[30].

(iii) Pitfalls and limitations:

Following limitations of pulse oximeter is to remember during its applications:

Dyshaemoglobinemias-Accuracy of pulse oximetry is excellent when oxygen saturation ranges from 70% to 100%, provided haemoblobin present in blood are reduced haemoglobin or oxygeneted haemoglobin. If carboxyhemoglobin or methaemoglogin are present, accuracy is affected[29].

Poor purfusion-Adequate arterial pulsation is needed to distinguish the light absorbed by venous blood and tissue. Reading may be unreliable or unavailable if there is loss of diminution of peripheral pulse[29]. Pulse oximeter works properly if pulse pressure is >20 mmHg or systolic BP>30 mmHg[21].

Motion artifact-Motion of sensor relative to skin can cause an artifact that the pulse-oximeter is unable to differentiate arterial pulsation[29]. Now a day's various methods have been developed to reject motion artifact[27]. Sensor may perform poorly if there is excessive movement of concerned part of neonate[31]

Pressure on the sensor- Pressure on sensor may result in inaccurate SpO_2 readings without affecting pulse rate determination[29].

Hyperemia; In this condition capillary and venous blood becomes pulsatile, resulting decrease in accuracy[29].

Abnormal dye-Pigments like methylen blue, severe hyperbilirubinaemia may interfere readings of pulse-oximetry[32].

High oxygen partial pressures: At high saturations, small changes in saturation are associated with relatively large changes in PaO_2.Thus the pulse oximeter has a limited ability to distinguish high but safe levels of arterial oxygen from excess oxygenation, which may be harmful as in premature newborns[29].

Hypoxic events: Delay response in hypoxic events are related to location of sensor. Desaturation is detected earlier when the sensor is placed more centrally. Lag time increases with poor perfusion. Venous obstruction, peripheral vasoconstriction and hypothermia delay detection of hypoxia[29].

Electrical interference: Electrical interference from an electro-surgical unit can cause the oximeter to give an incorrect pulse count or to falsely register decrease in oxygen saturation[29].

Light: One important problem is light. A photo diode used as light detector in pulse oximeter sensor produces current when any light hits it. It can not tell whether the light is coming from the red or infrared light emitting diodes(LED) of the pulse oximeter sensor or from room bright light[33].

Other factors: Severe anemia, superficial pigments, black colour of infant is a problem in readings of pulse-oximetry[32].

5. Transcutaneous oxygen (t_cPo_2) monitoring:

Here, partial pressure of oxygen is measured from skin surface by an electrochemical sensor[18]. The sensor is affixed over the chest or upper abdomen[3]. Oxygen diffuses through a membrane into the electrode, when it is reduced, setting up an electric current[21]. The skin surface is heated to 43.5° to 44°c to maximize skin surface blood flow[16]. The electrical current is related to partial pressure of oxygen (PaO_2) and is displayed as transcutaneous Po_2 ($TcPO_2$)[21].The transcutaneous PaO_2 values are quite reliable and comparable to simultaneous PaO_2, which should be crosschecked every 4 to 6 hours. Sensor site is to be changed every 2 hourly due to risk of skin burn[3]. Correlation with PaO_2 is poor in neonate with circulatory insuffiency and if operated at low sensor temperature[16]. Right to left shunt at ductal level may be evaluated by placing one skin sensor over right upper chest (preductal) and another sensor over left lower abdomen (postductal). A discrepancy of >20 % in $TcPO_2$ is indicative of significant right to left shunt[3].

Conclusion:

Oxygen supplementation is a common practice in newborn care. There are specific indications and methods of oxygen therapy in neonate. Oxygen therapy should be very judicious. Inappropriate supplementation of oxygen may not correct hypoxia or may lead to development of hyperoxia. Both hypoxia and hyperoxia are injurious to neonatal health. During oxygen therapy, SpO_2 value and more precisely the PaO_2 value on neonate should be maintained within a target able range. There are some monitoring methods of oxygen status in neonate. Control of oxygenation may be conveniently achieved within a target range with pulse oximeter. During use of pulse oximeter, it is very important to remember its limitations and pitfalls. In addition to continuous pulse oximetry, time to time PaO_2 monitoring through arterial blood gas analysis is important.

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