

Resuscitation of extremely preterm infants - controversies and current evidence

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Abstract

Despite significant advances in perinatal medicine, the management of extremely preterm infants in the delivery room remains a challenge. There is an increasing evidence for improved outcomes regarding the resuscitation and stabilisation of extremely preterm

infants but there is a lack of evidence in the periviable (gestational age 23-25 wk) preterm subgroup. Presence of an experienced team during the delivery of extremely preterm infant to improve outcome is reviewed. Adaptation from foetal to neonatal cardiorespiratory haemodynamics is dependent on establishing an optimal functional residual capacity in the extremely preterm infants, thus enabling adequate gas exchange. There is sufficient evidence for a gentle approach to stabilisation of these fragile infants in the delivery room. Evidence for antenatal steroids especially in the periviable infants, delayed cord clamping, strategies to establish optimal functional residual capacity, importance of temperature control and oxygenation in delivery room in extremely premature infants is reviewed in this article.

Key words: Extremely preterm infants; Resuscitation; Antenatal steroids; Delayed cord clamping; Ventilator support; Oxygenation in delivery room; Temperature stability

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Core tip: Management of extremely preterm resuscitation is one of the most challenging aspects of perinatal medicine. There is increasing evidence towards a trend for a more gentle measure of resuscitation to avoid injury both immediate and long term. In this article, we review the evolving strategies to aid the complex process of adaption to extra uterine life for extreme preterm infants.

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INTRODUCTION

The physiological adaptation to extra uterine life for a preterm neonate involves a series of complex processes, it is more pronounced in extremely preterm gestation (gestational age less than 27 wk)^[1]. Aerating the fluid filled lung and thereby attaining an adequate functional residual capacity, ability to perform gas exchange and switching to an oxygen enriched metabolism, establishing adult type circulation with stable haemodynamics along with maintaining body temperature are some of the key processes that occur within the first few minutes of life in any new-born^[2]. Furthermore, in the extremely preterm infants there is an overriding need for intervention to enable them to adapt to the above processes. Periviable infants are fragile and have many features that increase the difficulty of stabilisation immediately after birth.

Experimental and clinical studies done in past few decades related to resuscitation of preterm infants have shown that interventions by trained personnel during this critical period can not only improve immediate survival but also reduce long term morbidity^[3,4]. There is also growing evidence that some of these interventions can also trigger inflammatory and oxidative cascades injuring the organs, predisposing to long-term conditions^[3]. This evidence have supported in developing a trend towards gentle management in delivery room in the first "golden hour"^[5]. Data for stabilisation and resuscitation of periviable neonate is still limited. The aim of this article is to review the evolving approaches in resuscitation of extremely preterm infants. We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials and performed a manual search of references in narrative and systematic reviews. Search terms included "neonate", "newborn", "resuscitation", "delayed cord clamping", "antenatal steroids", "resuscitation of extremely preterm", "continuous positive airway pressure", and "sustained inflation".

DISCUSSION

Having an experienced neonatal resuscitation team during delivery, for appropriate stabilisation and resuscitation, improve outcome^[6-9]. Multiple studies have demonstrated improved outcomes for very low birth weight babies born in tertiary care centres vs out born infants^[6-9]. The combined risk of death and major morbidities such as neuro-disability at 36 wk, chronic lung disease and hospital stay in extremely low birth weight (500-999 g) infants born in tertiary maternity hospitals as compared to non-tertiary centres has recently been reported (OR = 3.86; 95%CI: 2.21-6.76) in a large cohort by Binder *et al*^[6].

Antenatal steroids

Antenatal corticosteroids have been proven to accelerate foetal lung development and reduce neonatal

morbidity and mortality when given between 28 and 34 wk of gestation^[6]. However, there is only limited research to guide their use in the peri-viable period (22-26 wk gestational age). To date, there have been 6 prospective and retrospective cohort studies evaluating ante-natal corticosteroids use in the periviable period (Table 1); these studies have used the same dosing schedule of betamethasone as the antenatal steroid.

Majority of these studies exhibited OR for neonatal death of 0.6 with antenatal steroid treatment, which is the same relative benefit demonstrated for corticosteroid use in later gestation. Amongst infants born at < 26 wk of gestational age, 7-9 mothers need to receive antenatal steroids to prevent 1 neonatal death. In this group of infants use of antenatal steroids have also been shown to reduce the incidence of intra-ventricular haemorrhage (IVH) as an outcome. Tyson *et al*^[11] have looked at the follow-up of periviable infants exposed to antenatal corticosteroids compared to those not treated with steroids. They demonstrated that when evaluated at 18-22 mo, the infants that delivered between 22 and 25 wk of gestation continued to demonstrate a reduction in mortality (OR = 0.55; 95%CI: 0.45-0.66). One must remain cautious while making decisions based on cohort studies, which have the potential for unintended bias. While further studies such as randomised clinical trials would be beneficial, the current available evidence strongly suggest that antenatal corticosteroids have value when given in the periviable period and should be offered when clinically appropriate. This benefit is clear from 23 wk onwards as seen by the above studies. It is less certain whether they should be utilized at 22 wk or less due to lack to data in this gestation. Because of the uncertainty in gestational age prediction, it is suggested that they should be used at this gestational age if preterm birth appears to be imminent.

Delivery room resuscitation

Delayed umbilical cord clamping: Delaying umbilical cord clamping in term infants is generally considered to be beneficial^[16]. The evidence for benefit of delayed cord clamping in preterm infants is not clear. Maintaining blood supply to heart while pulmonary vascular system gets replenished contributes to keeping an adequate left ventricular output, thereby avoiding reduced blood flow to the brain, coronary arteries, kidneys and rest of the body^[17]. A systematic review by Rabe *et al*^[16] reviewed 15 studies on delayed cord clamping in preterm infants. They concluded that providing additional placental blood to the preterm infants by delaying cord clamping for 30 to 120 s, rather than early clamping, seems to be associated with less need for transfusion, better circulatory stability, less IVH (all grades) and lower risk for necrotising enterocolitis (NEC). However primary outcomes of death as well as death or neuro-disability at 2-3 years were inconclusive. The optimal

Table 1 Studies reporting the outcomes of antenatal steroid use in periviable births

Ref.	Year published	Country of origin	No. of babies	Birth weight (g)	Gestational age (GA)	Mortality OR (95%CI)	IVH OR (95%CI)
Costeloe <i>et al</i> ^[10]	2000	United Kingdom	811	400-1000	< 26 wk	0.6 (0.34-0.89)	0.39 (0.2-1.0)
Tyson <i>et al</i> ^[11]	2008	United States	4446	400-900	< 26 wk	0.6 (0.23-0.78)	-
Hayes <i>et al</i> ^[12]	2008	United States	450	400-550	< 23 wk	0.3 (0.2-0.65)	-
Mori <i>et al</i> ^[13]	2011	Japan	11607	400-1000	< 26 wk	0.7 (0.44-1.24)	0.65 (0.21-1.68)
Bader <i>et al</i> ^[14]	2010	Israel	3450	400-1000	< 26 wk	0.6 (0.4-0.68)	-
Carlo <i>et al</i> ^[15]	2011	United States	10541	400-1000	22-25 wk	0.58 (0.52-0.65)	0.55 (0.50-0.62)

OR: Odds ratio; IVH: Intra-ventricular haemorrhage.

time to clamp the umbilical cord remains controversial. In all the studies, early clamping was defined as less than 15 s, the definition of late clamping was varied from more than 30 s to 3 min. There are several small randomized control trials that have compared early (< 15 s) with late clamping (> 30 s) following preterm birth and there are several prospective observational studies^[18-22]. However, there is limited data in periviable or non-vigorous preterm infants demonstrating improved mortality and morbidity following delayed umbilical cord clamping. A recent experimental study in lamb model demonstrated the effects of early vs delayed cord clamping on transitional haemodynamics^[23]. They reported that delayed cord clamping after initiation of positive pressure ventilation and establishment of functional residual capacity markedly improved cardiovascular function by increasing the pulmonary blood flow and stabilising the cerebral haemodynamics transition.

Although experimental studies support delayed cord clamping having a positive effect on the preterm, the setup needed to practically perform resuscitation manoeuvres with an intact cord still remains an impediment. There is lack of evidence for delayed cord clamping in a preterm who is moderately depressed. An alternative to this of cord milking has been suggested as a more rapid method to influence placental transfusion^[16,23,24]. This technique requires clamping the cord near the placenta and stripping around 20 centimetres, 2-4 times, from placental to foetal side. This can be performed within a few seconds. There have been five randomised control trials have been performed in preterm infants, but only with small number of preterm infants^[24-28]. Rabe *et al*^[24], Hosono *et al*^[25] and March *et al*^[26] have looked at need for the blood transfusions and the number in preterm babies, while Takami *et al*^[27] and Katheria *et al*^[28] have looked at haemodynamics following milking of cords. Further larger studies are needed for this procedure. There are some concerns that milking might not replicate the haemodynamic benefits of delayed cord clamping^[29]. Retrospective studies have shown Haemoglobin levels at birth of > 12 g/dL results in reduced mortality and improved morbidity in preterm infants < 32 wk of gestational age^[30,31].

Several trials are currently on-going for both

delayed cord clamping in preterm infants as well as for milking of cord as an alternative^[32,33]. A recent multicentre feasibility study of delayed cord clamping in preterm infants less than 32 wk gestation in United Kingdom (United Kingdom CORD trial) has compared early < 20 s to delayed cord clamping for at least 2 min. The study has been concluded and the results are awaited^[32]. A large randomised trial is currently been undertaken in Australia which is nearing completion of recruitment^[33]. The CORD trial will contribute to an international collaborative individual patient meta-analysis of similar trials of enhanced placental transfusion, including the Australian Placental Transfusion trial. Altogether, these trials will enrol 2000-5000 very preterm infants, which are expected to improve our current understanding and evidence of delayed cord clamping in these infants and its impact on survival and neurodevelopment in childhood.

Stabilising temperature of preterm infants:

Preterm infants lack adequate brown adipose tissue and therefore cannot activate thermogenesis. They quickly lose heat in the delivery room by evaporation of amniotic fluid, by conduction of heat from the body touching cool surfaces, by convection and radiation to cooler surroundings. They are highly susceptible to hypothermia unless preventive efforts are made. A study has shown that for every 1 °C below 36 °C on admission temperature, mortality increases by 28%^[34]. Increasing the ambient temperature of delivery room to at least 26 °C before the delivery is an important intervention^[35]. Both hypothermia and hyperthermia during stabilisation can be detrimental^[36]. All extremely preterm infants should be brought in the resuscitaire under radiant heat and wrapped in polyethylene or polyurethane bags or wrap, up to their shoulders without drying^[37-39]. This reduces heat loss and maintains adequate humidity. All subsequent stabilisation and assessment should be done through the plastic bag. Multiple studies have shown that plastic bags improve temperature upon admission^[39,40] but there are no studies powered for clinical outcomes like death and long term neurodevelopmental outcome^[40]. Preterm infants can be placed on a chemically activated thermal mattress in combination^[41]. The head should be

Table 2 Overview of the results of the studies comparing continuous positive airway pressure and invasive ventilation

Ref.	Total number	Gestational age (GA) in wk	Death or BPD CPAP	Death or BPD non CPAP	Death or BPD relative risk (95%CI)	Days needing mechanical ventilation CPAP	Days needing mechanical ventilation non CPAP	Days needing mechanical ventilation <i>P</i> value
Morley <i>et al</i> ^[51]	610	25-28	108/307	118/303	0.9 (0.73-1.11)	0-11	11-14	< 0.001
SUPPORT ^[52]	1316	24-27	323/663	353/653	0.9 (0.81-1.00)	2-32	2-36	0.01
Sandri <i>et al</i> ^[54]	208	25-28	53/103	32/105	1.01 (0.7-1.57)	1-14	1-18	< 0.01
Dunn <i>et al</i> ^[53]	648	26-29	68/223	138/425	0.94 (0.74-1.19)	1-8	1-10	0.01

Infants randomised to prophylactic surfactant group and intubate, surfactant, or extubate group were combined in the intubation group. CPAP: Continuous positive airway pressure; BPD: Bronchopulmonary dysplasia.

covered by a hat. Care should also be taken to ensure that hyperthermia is avoided. Monitoring infants' temperature is of paramount importance. Perinatal hyperthermia is associated with respiratory depression as well as risk of adverse neurological outcome^[36]. Every hospital delivering high risk infants should have protocols for controlling delivery room temperature, systematic use of plastic bags and hats, monitoring temperature during stabilisation and transport to avoid hypothermia or hyperthermia. Admission temperature is an integral part of the Clinical risk Index for Babies II (CRIB II) score. The CRIB score was developed to predict mortality for infants born at less than 32 wk gestation at birth and was derived using data from infants admitted to four UK tertiary neonatal units from 1988 to 1990^[42]. This score has been widely used to quantify the risk of mortality among very preterm infants^[42]; it is assessed in the first 12 h of birth. The CRIB score was modified in 2003 as CRIB II score^[43], where gestational age and birth weight together with admission temperature and base excess were added to predict mortality. The new score was intended to improve predictions for smaller, very premature infants and to exclude variables that could be influenced by care given to the infant. Score for acute neonatal physiology (SNAP) is another mortality prediction score developed in United States^[44] a simpler version called SNAP II was developed later using data from 30 American units^[45]. Admission temperature was one of the important components of these mortality prediction scores.

Respiratory support in stabilisation

Ventilatory support: Despite considerable advances in perinatal-neonatal care, there is a trend for increased incidence of bronchopulmonary dysplasia among survivors of prematurity^[46,47]. Appropriate respiratory support in the delivery room can ensure reduction in the damage caused to the lungs. Preterm infants are unique due to their poor respiratory drive, structurally immature lungs, surfactant deficiency and highly non-compliant chest wall. Respiratory support should improve lung compliance thereby achieving adequate minute ventilation, decrease work of breathing and provide assisted ventilation as required. In order to ensure good gas exchange, consistent

functional capacity has to be established, while avoiding areas of atelectasis and over distension.

Use of positive end expiratory pressure (PEEP) during intermittent positive pressure ventilation (IPPV) or use of continuous positive airway pressure (CPAP) alone, after birth to facilitate alveolar recruitment and to avoid barotrauma and volutrauma from mechanical ventilation is recommended^[48]. CPAP can help establish and maintain a functional residual capacity in preterm lung, thereby improving pulmonary haemodynamics and respiratory distress^[48]. Most neonatal resuscitation guidelines (NRP/NLS) have supported the use of CPAP as a mode of ventilator support for preterm babies soon after birth^[49].

A systematic review with meta-analysis in 2013 by Schmölder *et al*^[50] evaluated the difference of outcomes between invasive and non-invasive respiratory support in preterm infants at birth. Four randomised controlled trials were evaluated and they concluded that nasal CPAP initiated in the delivery room compared with intubation reduces death or bronchopulmonary dysplasia in very preterm babies (Table 2)^[51-54]. The meta-analysis suggested that one additional infant could survive to 36 wk without bronchopulmonary dysplasia for every 25 babies treated with nasal CPAP in the delivery room rather than being intubated and mechanically ventilated. Pooled analysis showed a significant benefit for the combined outcome of death or bronchopulmonary dysplasia, or both, at 36 wk corrected gestation for babies treated with nasal CPAP: RR = 0.91; 95%CI: 0.84-0.99; RD = -0.04; 95%CI: -0.07 to -0.00; NNT of 25.

However none of these trials included infants less than 23 wk and only 1 trial had infants at 24 wk gestation. There are four small studies in periviable babies comparing invasive and non-invasive ventilation. Finer *et al*^[55] demonstrated that although about half of 24 wk GA infants can be stabilised on CPAP in the delivery room, very few infants of less than 24 wk GA avoided delivery room intubation.

These trials indicate that despite a strategy of CPAP use after birth in extremely low gestational age infants, rates of bronchopulmonary dysplasia (BPD) or death at 36 wk postmenstrual age (PMA) remain high, ranging from 41% to 64%^[52,56,57].

CPAP should not be used in place of positive

pressure ventilation when respiratory effort is poor or absent^[54,58]. In a recent study, it was shown that a stepwise PEEP strategy after birth improved gas exchange, lung mechanics and end expiratory volume without increasing lung injury in preterm lambs^[59].

Sustained inflation (SI) has been suggested as an alternative to CPAP. Sustained inflation is application of higher pressure (25 cm H₂O) for a prolonged time than normal (15-25 s)^[60]. A systemic review in 2014 by Schmölzer *et al*^[61] compared sustained inflation vs positive pressure ventilation. Four RCTs were analysed showing SI improves functional residual capacity (FRC) and therefore the need for mechanical ventilation during the first 72 h, the pulmonary protective effect is lost in the subsequent development to BPD^[62-65]. Further clinical trials are required to evaluate the efficacy, including risk of pneumothorax, long term outcomes and safety, of this lung aeration manoeuvre at birth.

The Sustained Aeration of Lung (SAIL) trial, a large, international multi-centred randomised trial is currently on-going evaluating sustained inflation vs positive pressure ventilation^[66]. This prospective randomized controlled unblinded trial will recruit 600 infants of 23 to 26 wk gestational age who require respiratory support at birth. Infants in both arms will be treated with PEEP 5 to 7 cm H₂O throughout the resuscitation. The study intervention consists of performing an initial SI (20 cm H₂O for 15 s) followed by a second SI (25 cm H₂O for 15 s), and then PEEP with or without IPPV, as needed. The control group will be treated with initial IPPV with PEEP. The primary outcome is the composite outcome of bronchopulmonary dysplasia or death at 36 wk post-menstrual age.

Oxygenation in delivery room: Preterm infants are deficient in anti-oxidative protection and are highly susceptible to oxygen toxicity thereby exacerbating morbidities^[67]. Avoiding hypoxemia and hyperoxaemia during resuscitation is essential. Blended oxygen and pulse oximetry play an important role in titrating the delivery of oxygen. Due to inherent technology behind the pulse oximetry measurements saturation values less than 60%-70% are inaccurate^[68]. Pulse oximetry should be placed on the right hand or arm to evaluate the pre-ductal oxygen levels; it also measures heart rate accurately, which helps in the resuscitation. The optimal initial fraction of inspired oxygen (FiO₂) for resuscitating/stabilising premature infants is not known. A recent meta-analysis by Saugstad *et al*^[69] in 2014 for optimal initial fraction of oxygen in less than 32 wk gestation analysed 10 published studies covering 677 infants. It shows that the outcomes of starting with a low initial FiO₂ (0.21-0.30) were as good as starting with a high FiO₂ (0.6-1.0). Oxygen should be individually titrated based on the neonate's response.

Harling *et al*^[70] performed the first resuscitation trial

of infants of less than 31 wk GA with either 50% or 100% oxygen for the entire time of the resuscitation and found no significant differences in cytokines, death, or survival without BPD. All subsequent trials in preterm infants comparing a high vs low oxygen concentration utilized a targeted oxygen saturation strategy. The room air vs oxygen administration in preterm Resuscitation (ROAR) study randomised 106 infants \leq 32 wk gestation comparing three O₂ strategies: 100% throughout (High oxygen group), 100% initially (Moderate oxygen group) and 21% (Low oxygen group) initially. The last two groups had the FiO₂ titrated until a SpO₂ of 85% to 92% was reached^[71]. This study demonstrated that targeting resuscitation SpO₂ values was feasible for very preterm infants. Ezaki *et al*^[72] studied infants < 35 wk' gestation born by caesarean section. Twenty one infants received 100% oxygen and 23 were treated with a targeted oxygen saturation strategy. They reported lower 5 min Apgar scores, and higher total hydro peroxides in the 100% oxygen group which implies an improved outcome with targeted oxygen saturation strategy. None of the studies have evaluated long term outcomes in these infants, which is of utmost importance. That is why larger prospective randomised controlled trials with long term outcome measures are required.

There are several experimental and clinical studies to assess the initial oxygen concentration during resuscitation^[73,74]. The To2pido (Targeted oxygenation in the resuscitation of premature infants and their developmental outcome) study is an international, multicentre trial currently set up in Australia, Malaysia, and Singapore and with centres starting in India^[75]. It is to determine the outcome of very premature infants (< 30.6 wk gestation) who have had resuscitation at birth starting with either room air or 100% oxygen. The trial is currently recruiting and the target number of infants to be recruited is 1892. The primary outcome is said to be death at 2 years and secondary outcomes are evidence of bronchopulmonary dysplasia at 36 wk gestation or major disability at 2 years of age. The Premature Infants Resuscitated with Oxygen or Air (PRESOX) trial, which is planning to recruit 1260 infants, is a prospective randomized clinical trial of extremely premature infants that will assess the use of a low and high oxygen concentration for the initial resuscitation^[76]. This proposed trial will use targeted oxygen saturation levels over the first 15 to 20 min of life to compare a low and a higher initial oxygen level for the resuscitation of such infants, and is powered to evaluate short term outcomes of survival without oxygen at 36 wk and survival without retinopathy of prematurity, and the long term outcome of survival without significant neurodevelopmental impairment at 2 years of age.

In 2010, Dawson *et al*^[75] developed SpO₂ reference range for the first ten min of term, preterm and extremely preterm infants. Three databases were merged, two from Australia and one from Spain to

evolve this range. At present Dawson's nomogram is the best available reference range for titration of oxygen in preterm infants. However it should be noted that the reference range was based on the infants who were breathing in air. A study by Vento *et al.*^[76] in 2013 showed that preterm infants requiring CPAP but in air attained higher saturation significantly earlier than in Dawson's nomogram.

There is growing interest in monitoring CO₂ levels in delivery room and using it as a tool for assessment of functional residual capacity. A systematic review in 2014 by Hawkes *et al.*^[77] reviewed the current evidence for CO₂ monitoring. These mainly included observational studies with only one RCT. Observational studies have a higher degree of bias and can also mask cause and effect relationships or, alternatively, suggest correlations where there are none. The conclusion was that CO₂ detection may be of particular benefit for preterm infants in the delivery suite. However, there is a need for further research into CO₂ detection, in particular, capnography, as a means of confirming effective IPPV in neonatal resuscitation.

CONCLUSION

Resuscitation and stabilisation of a preterm neonate consists of complex decisions and tasks undertaken by the team. In recent years, there is growing evidence for providing a gentle, least invasive support in the delivery room to reduce immediate and long term morbidities. There needs to be further research in all the aspects of resuscitation especially for periviable neonate.

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