Optimising Intravenous Volume Resuscitation of the Newborn in the Delivery Room: Practical Considerations and Gaps in Knowledge

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Keywords

Asphyxia · Cord blood · Delivery · Newborn resuscitation · Neonatal haemodynamics · Shock

Abstract

Volume resuscitation (VR) for the treatment of newborn shock is a rare but potentially lifesaving intervention. Conducting clinical studies to assess the effectiveness of VR in the delivery room during newborn stabilization is challenging. We review the available literature and current management guidelines to determine which infants will benefit from VR, the frequency of VR, and the choice of agents used. In addition, the potential role for placental transfusion in the prevention of newborn shock is explored.

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Introduction

The neonatal resuscitation section of the “2015 International Liaison Committee on Resuscitation (ILCOR) Recommendations” was recently published [1]. These

recommendations provide updated evidence on a number of key areas of newborn management in the delivery room (DR), and there is now a sizable body of evidence supporting many aspects of support in the DR. However, a number of outstanding issues remain unresolved, outlined in the “2010 PICO Questions Not Reviewed” in the 2015 section of the above mentioned consensus document [1]. In particular, whilst up to 10% of newborns require assistance with breathing at birth, the use of chest compression, medication administration, and fluid bolus volume resuscitation (VR) occurs significantly less frequently and is not as well studied [2].

Prospective studies evaluating VR during newborn stabilization remain impracticable as the frequency of VR in this population is very low, and it may be challenging to withhold fluid as a control measure in such circumstances. Also, whilst short-term outcome measurements are possible, it is difficult to ascribe robust long-term outcome measures to a single intervention during DR stabilization. Unnecessary VR in the setting of asphyxia has the potential for harm. Nonetheless, the question of the adequacy of VR during stabilization of the newborn infant arises relatively frequently.

Table 1. Objective monitors for assessing newborn circulatory status in the DR

	Normative values established for term infants ¹	Normative values established for preterm infants ²	Accuracy	Comments
Pulse oximetry HR	+	+	+	gold standard monitor for assessing HR in the DR; may be unreliable during CPR
ECG HR	+	+	+	quicker data acquisition than pulse oximetry but may require extra personnel
Doppler US HR	+	+	+	a novel method for accurate data acquisition but extra trained personnel required
BP	+	–	–	accurate measurements not feasible in the DR setting
ECHO-LVO/RVO	+	–	+	supplies valuable information but extra trained personnel required
NICOM-LVO	+	–	–	limited as only trends in CO can be appreciated; further studies advised

BP, blood pressure; CO, cardiac output; DR, delivery room; ECHO, echocardiogram; ECG, electrocardiogram; HR, heart rate; LVO, left ventricular output; RVO, right ventricular output; NICOM, non-invasive cardiac-output monitoring; US, ultrasound.

¹ In the immediate newborn period; ² <32 weeks' gestation in the immediate newborn period.

We reviewed the current available literature on this important aspect of newborn care, in an effort to uncover the evidence to support the use of VR in the DR. We reviewed (1) how to determine which infants may benefit from VR, (2) the indication and frequency of VR in the DR, (3) which fluid should be used, and, lastly (4) whether there is a role for placental transfusion in such infants.

How to Determine Which Infants Require VR

In newborn term and preterm infants, the practice of VR is often considered to be beneficial, for instance, in severe arterial hypotension or severe metabolic acidosis in the context of neonatal shock [2, 3]. Shock is caused by an acute failure of circulatory function and is characterized by inadequate tissue and organ perfusion [4], and is most commonly caused by an asphyxial insult and/or hypovolaemia in newborn infants where there may/may not be obvious blood loss and also in the setting of sepsis.

VR can be lifesaving for newborn infants with hypovolaemic shock or sepsis. However, infants who sustain an acute perinatal asphyxial insult, not secondary to acute blood loss, are generally euvolaemic [2]. In cases of intra-uterine hypoxia, there is often an increased blood volume [5, 6]. VR in such infants may lead to volume overload

and worsen cardiovascular compromise in infants who may have impaired myocardial contractility [2, 7]. However, in a compromised term neonate in the DR, distinguishing an infant with hypovolaemic shock from a normovolaemic infant with asphyxia is challenging.

ILCOR advises clinical assessments of peripheral perfusion to differentiate between the normovolaemic and hypovolaemic state [1]. In the 2010 ILCOR report as well as in the 2015 European Resuscitation Committee (ERC) guidelines, the colour of the mucous membranes was said to be a useful clinical discriminator [8, 9]. In the case of hypovolaemic shock, these membranes will be pale, but in the case of asphyxia, they may have a “normal” colour [10]. However, assessments such as capillary refill time, colour, and palpation of peripheral pulses are subjective, and there can be significant inter-rater variability, as highlighted by several investigators [11, 12]. Assessments based on the colour of the mucous membranes, although specific if oxygen saturations are <70%, are still subjective, and are associated with a low sensitivity [13], making it difficult to clinically determine the underlying aetiology of newborn shock.

Objective measures of newborn circulatory status are an important component of assessing infants with shock in the DR, both for diagnosing circulatory failure and to monitor the response to treatment. We will discuss the

methods used for heart rate (HR) and blood pressure (BP) assessment in the DR, and also newer modalities such as echocardiography (ECHO), perfusion index (PI), and non-invasive cardiac monitoring (NICOM) (Table 1).

Assessment of newborn HR has been the mainstay to assess effective newborn transition and to gauge the need for resuscitatory interventions in the DR [1]. Methodologies include assessment by stethoscope auscultation, palpation, pulse oximetry, electrocardiogram (ECG), and Doppler ultrasound. While the clinical assessment of HR by auscultation at the apex with a stethoscope is more accurate than the assessment of umbilical pulsations [14], these methodologies are often inaccurate compared with other objective methods, such as pulse oximetry and ECG [9]. A recent commentary has highlighted that a prolonged time period to auscultate may provide a more accurate HR [15].

Assessing HR from pulse oximetry readings provides real-time accurate information [16], but there can be delays in signal acquisition of between 1 and 2 min [17], and especially in low-perfusion states [18]. Whilst pulse oximetry is easy to apply by using a single probe, preferably on the right hand (pre-ductal) of the neonate, in depressed neonates with poor cardiac output, lack of signal may be confused with handling errors or device failure, and hence distract from managing the clinical state of the infant. In addition to the HR, pulse oximetry also provides oxygen saturation data on a continuous basis. Similarly to the abovementioned errors associated with obtaining oxygen saturation signals, pulse oximetry-derived HR can be adversely affected by improper application, movement artifact, or poor peripheral perfusion, and so may not be reliable while performing chest compressions [19].

Evaluation of the HR by means of ECG has been shown to provide more accurate HR values, in a shorter time than pulse oximetry HR in the DR, and it is less prone to movement artifact. Katheria et al. [20] reported median times for acquiring a signal from ECG and pulse oximetry of 4 and 32 s following application, respectively. However, obtaining an ECG requires the application of 3 chest leads; this may itself take up to 20s [20]. In practice, a baby's wet skin may also pose a challenge, as not all ECG leads stick well to a wet surface and so the task of applying the leads may require additional personnel. Furthermore, pulseless electrical activity can present with a visible ECG, but no cardiac output, even though this is an extremely rare occurrence in the newborn.

Hutchon [21] showed that measurement of the neonatal HR by Doppler ultrasound is possible, and can easily be seen as an extension of fetal HR monitoring until pulse

oximetry readings are available. Measurements are accurate and comparable with ECG HR values [22]. This approach may be challenging, as clinical expertise is required for accurate ultrasound assessments and, at present, continuous measurements are not practical. In conclusion, the assessment of HR is important. To date, the accuracy of routinely applied methods varies, with palpation and auscultation being the least accurate and ECG being the most accurate [23].

Neonatal oscillometric BP monitoring is another objective methodology that has been investigated during neonatal transition, although not widely used clinically. A number of studies have shown that BP measurements are obtainable in the DR [24, 25]. However, such non-invasive BP measurements are not reliably consistent, especially in preterm neonates, and invasive BP monitoring is not practical in the DR setting [3]. Thus, BP acquisition and values obtained in the DR may not be clinically useful in assessing the circulatory status of newborn infants.

A recent review identified 4 studies of cardiac-output ECHO monitoring during term newborn stabilization [24]. These studies confirm that ECHO assessment of neonatal transition (ductal haemodynamics, and changes in right and left ventricular outputs) is feasible as an objective adjunct to determining newborn haemodynamic status [26–28]. Normative ECHO values for left ventricular output and stroke volume in the first 15 min of life have been determined [27, 29]. Therefore, in theory, ECHO could help distinguish between infants who present with low-output cardiac failure in the setting of hypovolaemic shock, and high-output failure in the setting of asphyxia. However, studies have yet to assess whether ECHO analysis could help in determining the aetiology of newborn shock or volume responsiveness in the newborn period, and whether this approach is indeed useful to guide clinical decision-making [30].

Weisz et al. [31] described a method which provides non-invasive continuous cardiac-output monitoring (NICOM). This technology is based on the assumption that changes in the resistance to electrical currents captured by electrodes on the thorax are directly related to changes in aortic volume during different stages of the cardiac cycle. NICOM measurements correlate well with timed ECHO measurements in neonates [31]. However, NICOM underestimates the actual cardiac-output value (47% error reported) [31]. Therefore, it may be more useful in monitoring trends in cardiac output. It is not designed to help in discriminating between causes of newborn shock or volume responsiveness in the newborn period, and a systematic review of NICOM confirmed that

it is not accurate in determining volume responsiveness in paediatric patients [30]. Katheria et al. [32] documented increasing cardiac outputs on NICOM over the first 5 min of life in term infants during delayed umbilical-cord clamping, and, although feasible, at present, NICOM is not a valuable tool for assessing infants in the DR.

PI monitoring is a non-invasive method of assessing peripheral perfusion and provides continuous values. These values are derived from and displayed by a pulse oximeter, which utilizes an extra wavelength emission in its calculations to distinguish between the pulsatile and non-pulsatile components of arterial blood, and produces a real-time measure of peripheral perfusion [33]. The PI has been utilized to assess infants in a number of clinical domains in the NICU setting [34]. These include elective screening for congenital cardiac disease [35], predicting low systemic blood flow [36], and assessing perfusion following blood transfusion [37]. Values for PI are also easily obtained in the DR [38]. However, they are highly variable in the immediate newborn period, for both term and preterm infants, which limits the use of PI in assessing newborn circulatory status in the DR [38, 39].

Near-infrared spectroscopy (NIRS) may be a useful adjunct, and there have been a number of recent DR-orientated studies addressing the use of NIRS [40, 41]. It is easy to apply and there is very little delay in signal acquisition. NIRS has been utilized to assess the adequacy of peripheral oxygenation [42]. Wardle et al. [43] evaluated oxygen delivery and consumption in the forearm of 30 preterm babies, 15 of whom were hypotensive by Watkins criteria. They identified a lower oxygen delivery and consumption in the hypotensive babies. However, NIRS has yet to demonstrate that its use results in improved outcomes for term and preterm infants.

In summary, there appears to be no single failsafe or reliable clinical or electronic modality that accurately delineates haemodynamic status in the healthy or sick neonate during transition. Objective HR assessment remains important. The typical description of acute blood loss or hypovolaemic circulation has been that “pallor of the mucous membranes and skin is nearly always present” [44, 45]. We contend that this clinical sign is a very poor discriminator between acute blood loss and asphyxia, and that the utilization of other objective parameters (BP, ECHO, NICOM, and PI) may allow for better discrimination between these 2 broad categories in the future. However, the sensitivity and specificity of these parameters, individually or collectively, remains to be determined.

The Frequency of VR in the DR

Although the incidence of neonatal shock remains unknown, <1% of newborn infants require advanced resuscitative measures, including chest compression, drug administration, and fluid boluses during newborn stabilization [46]. Wyckoff et al. [2] described a cohort of 37,972 infants of >34 weeks' gestation delivered over a 30-month period, 28 of whom (0.07%) received intensive CPR. This was defined as the need for >60 s of positive pressure ventilation and chest compressions, with or without the administration of medications. Five infants did not respond to these interventions (including VR in at least 4 of these cases) and died in the DR. Of the remaining 23 infants admitted to the NICU, 13 had received VR. Therefore, in this cohort of infants delivered at >34 weeks' gestation, only 0.04% (4.4/10,000) received VR in the DR. The authors compared the infants that had received VR ($n = 13$) with those who had not ($n = 10$). The patients who received volume were more likely to have low Apgar scores (Apgar <2 at 5 and 10 min), to have a lower cord pH, and to have received adrenaline in the DR and their mean resuscitation times were longer in duration (8 vs. 4 min). The mean BP on admission was lower (32 vs. 49 mm Hg) and initial haematocrit was also lower (41 vs. 54) in the group who received volume. In the 13 infants who received VR, the clinical indication for the initial use of volume was an inadequate HR despite CPR and adrenaline administration in 10 cases, and poor perfusion coupled with a clinical suspicion of acute blood loss in the other 3. It is difficult to tease out the underlying aetiology of shock from this retrospective study, other than to say that the majority of infants who received volume were hypotensive on arrival to the NICU, but the majority of those who did not receive volume were not. The aetiology of newborn shock is multifactorial, and determining the difference between acute blood loss and asphyxia based on BP values upon admission is challenging. From this retrospective study, one can conclude that sicker babies (lower Apgar score, lower cord pH, in receipt of adrenaline) are more likely to receive VR, which is consistent with current resuscitation guidelines.

Overall, there is rather limited information available and there are no comparative studies to assess variations in practice between neonatal centers. We know that VR is rare, but there is a paucity of available research to quantify just how often it occurs. Future resuscitation committees should reach a consensus on a definition for newborn shock if studies are to be of value. Without further data, it will be challenging to perform comparative studies or best-practice reviews on VR in the DR.

Table 2. Volume resuscitation agents in hypovolaemic shock

	Availability	Efficacy	Risk	Cost	Recommendation
O-Rhesus-negative blood	centre-dependent	most efficacious	low	a valuable resource	gold standard treatment for hypovolaemic shock
Crystalloid (NaCl 0.9%)	readily	equal to albumin	none	–	first-line agent when whole blood is not available
Albumin	readily	equal to crystalloid and synthetic volume expander	low	+	not recommended
Synthetic volume expander	readily	equal to albumin	low	+	not recommended

What Agent Should Be Administered in Hypovolaemic Neonates?

International guidelines generally advise that, when hypovolaemic shock is suspected, emergency un-cross-matched O-Rhesus-negative blood should be administered whenever available (Table 2) [1]. If not, isotonic crystalloid fluids should be given. Colloid infusions such as albumin are no longer advised as a treatment option during DR stabilizations [9, 44]. However, the suggestion stems from extrapolation of data from studies on animal models and older children, as there is a paucity of neonatal or DR studies. The ideal amount to be transfused is unclear, but an initial 10–20 mL/kg may be appropriate, considering that DCC may result in an additional 30% blood transfer.

Whole blood provides volume, oxygen-carrying capacity, and colloids, and is the most rational agent to administer in the setting of acute blood loss. Transfusion of blood products carries a small risk of infectious transmission (in the order of viral contamination in 1/1–1.3 newborns) [47], which may be particularly harmful towards extremely-low-birth-weight infants who are already immunologically compromised and neurodevelopmentally vulnerable [48]. Haemolytic transfusion reactions are rare in newborn infants [49]. We recently reviewed our own practice (Medical Centre, University College Cork, Cork, Ireland) in relation to the administration of emergency un-cross-matched blood in the DR. Over a 5-year period, there were 42,657 births, and 6 infants (1.4/10,000 live births) received an emergency blood transfusion in the DR [50]. Neither delayed cord clamping nor milking was routinely practiced in our DR in this time frame. The indication for administration of whole blood was based on a non-response to intensive CPR and a history of pos-

sible blood loss (e.g., vasa previa, fetomaternal haemorrhage, or placental abruption). However, generally speaking, whole blood is not readily available and the administration of crystalloid occurs in the first instance. This figure is greater than the DR volume administration rate reported by Wyckoff et al. [2], where 3 infants received volume because of concerns about acute blood loss (0.8/10,000).

There is no data from DR resuscitations comparing the efficacy of crystalloid or colloid agents. Albumin is the most abundant protein in plasma, and, during normal homeostasis, is responsible for maintaining 60–80% of colloid osmotic pressure. Much of the data on crystalloid or colloid use has been derived from the management of preterm infants at risk of/with established hypotension [51]. Neonatal studies to date performed outside the DR setting have displayed no difference in efficacy between colloid and crystalloid infusions [52, 53], and crystalloids are generally the preferred agent for many practical reasons: they are readily available, cheaper, and carry a lower risk of infectious complications [45]. Synthetic colloid volume expanders are as effective as albumin, have no infectious risks, and are readily available [54]. However, they are also expensive compared to crystalloids, and concerns have been raised in the past regarding different solutions disturbing paediatric coagulation systems [55]. Therefore, when whole blood is not available, the administration of crystalloid volume is advised for the treatment of newborn hypovolaemic shock.

The volume to be infused and the rate of infusion have not been studied in neonates. However, it should be noted that there is animal data which raises a number of concerns related to the rapid administration of volume expanders [7, 56]. Wyckoff et al. [7] compared 5% albumin, normal saline, and no volume on the development

of pulmonary oedema and the restoration of mean arterial pressure during the resuscitation of asphyxiated piglets. Volume administration in these animals did not improve mean arterial BP. The authors demonstrated an increased risk of pulmonary oedema in the piglets when albumin was administered compared to the control animals. Another study evaluated the effect of rapid volume administration on coagulation haemostasis in piglets, comparing 4 different fluids including normal saline and albumin [56]. These piglets were not hypovolaemic. All fluids administered caused a significant weakening of clot strength, suggesting that rapid volume administration can impact upon the coagulation profile. Therefore, the potential side effects of the rapid administration of crystalloids or colloids in the DR setting need to be carefully considered.

Is There a Role for Placental Transfusion in Compromised Infants?

The 2015 ILCOR and ERC guidelines advocate delayed cord clamping (DCC, for at least 1 min) in uncompromised term and preterm infants [1, 9]. This is based on a plethora of benefits outlined in recent Cochrane reviews for both term and preterm infants, such as reduced incidences of anemia, hypotension, and intraventricular haemorrhage following DCC [57, 58]. However, the authors advise that, until further evidence is available, placental transfusion should be discontinued in infants who are not breathing, so that resuscitation measures are not delayed [1]. They acknowledge that even though there is compelling physiological data from animal studies to suggest many benefits to resuscitating depressed newborns whilst on the cord, such a recommendation has not been formulated in the ILCOR or ERC guidelines due to the lack of human studies on the feasibility and safety of this approach [59, 60]. First-in-human studies are currently underway.

Newborns that require resuscitation at birth are at a higher risk of brain injury and death, and some commentators have argued that these infants may receive the greatest benefit from DCC [61]. In the setting of hypovolaemic shock, fresh whole blood which supplies volume expansion, colloid expansion, and oxygen-carrying capacity may be considered an ideal agent [62]. The benefits of DCC are thought to result from a number of physiological processes that include (1) the placental transfer of blood, (2) accommodating a more stable haemodynamic transition from fetal life, and (3) a transfer of stem cells.

The volume and rate of delivery of placental blood as a result of DCC was thought to be increased if the infant was placed in a superior position relative to the placenta when uterine contractions are present and if newborn respiration has commenced [63–65]. However, recent studies suggest that the position of the newborn may not have much influence on the volume of blood transfused [66, 67]. Placental transfusion can result in a direct intravascular transfusion of 30–40% of the total neonatal blood volume [63–65, 68]. For infants with hypovolaemic shock, DCC could be an important first step in their resuscitation, if early identification was possible [69]. For preterm infants (<32 weeks' gestation), an increase in total blood volume results in higher BP and a reduced need for inotropic support, with no significant side effects [57]. Conversely, it is unknown whether asphyxiated infants will benefit from placental transfusion and whether DCC could be deleterious due to the potential for volume overload, polycythemia, and the possible delay in establishing positive pressure ventilation [70].

DCC may facilitate a more stable haemodynamic transition for compromised infants [61]. In preterm infants, it was associated with a 50% reduction in intraventricular haemorrhage (although not significant for grade 3 or 4), which can be explained by the increase in fluctuations of cardiac output which follow immediate cord clamping [57, 71, 72].

DCC also increases the transfer of haematopoietic stem cells, endothelial cell precursors, mesenchymal progenitors, and pluripotent lineage stem cells [73]. Stem cell therapies are under investigation for the early treatment of developmental brain injury, including perinatal asphyxia and preterm birth [74, 75]. The evidence to date supports that cord blood cells may provide neuro-protective benefits due to their actions on a range of complementary biochemical pathways that become dysregulated in response to perinatal asphyxia [76]. Autologous umbilical-cord blood mononuclear cells in asphyxiated newborn lamb and rat models restore normal brain metabolism, and reduce brain inflammation, astrogliosis, and neuronal apoptosis [74, 77, 78]. Studies to date have concentrated on autologous transfusions, and the placental transfusion of stem cells by DCC has yet to be studied *in vivo*. Therefore DCC for infants in need of resuscitation cannot be recommended based on the transfer of stem cells alone [76].

Strategies that allow for placental transfusions but do not delay resuscitative measures are currently under evaluation, as mentioned earlier. Newborn resuscitation at the bedside while the cord is still attached is now feasible

with the introduction of mobile resuscitation trolleys [79]. Another strategy that allows for placental transfusion at birth and does not delay neonatal resuscitation is umbilical-cord milking, which has the advantage of transfusing similar volumes without delaying routine neonatal resuscitation [80]. Short-term benefits similar to those with DCC for preterm infants have been reported [81]. However, there is still a dearth of knowledge about umbilical-cord milking, with concerns that multiple stripping of the cord could release harmful cytokines or cellular debris into the infant's circulation so, at present, guidelines do not recommend it following term or preterm deliveries [61].

While DCC may be appropriate when haemorrhagic shock is presumed, the same difficulties in distinguishing such infants from other compromised infants remain. Further research on stem cell transplants, bedside resuscitation measures, and umbilical-cord milking are warranted.

Conclusion

In a setting with presumed or obvious blood loss such as placental abruption or fetal-to-maternal transfusion, VR therapy may indeed have an important role to play. However, for other clinical scenarios such as asphyxia, the current set of clinical and technical tools makes it difficult to differentiate the haemodynamically compro-

mised infant who will benefit from volume therapy from the normovolaemic asphyxiated infant who may, potentially, be further compromised by volume therapy. When the decision to treat is made, fresh whole blood should be used if available, and crystalloid solutions if not. DCC remains the most obvious source for immediate transfusion in such infants but, currently, it is unknown if DCC is beneficial in the setting of haemorrhagic shock, and further work is needed to assess whether DCC with ventilatory support results in better outcomes for compromised infants at birth.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Source

This review was supported by a Science Foundation Ireland Research Centre Award (INFANT-12/RC/2272).

Author Contributions

E.M.D. conceived and designed the review. D.F. drafted the initial manuscript. All authors critically revised the manuscript for important academic content, agreed on the final draft, and approved its submission for publication.

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