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Drugs in the delivery room

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ABSTRACT

The need for cardiopulmonary resuscitation in newborns is quite rare, as most non-vigorous infants respond well to effective ventilation. For the minority of babies who do not respond to adequate ventilation, chest compressions are necessary using the preferred two thumb technique. Since effective ventilation remains a key component to successful resuscitation, chest compressions are coordinated with ventilations in a 3:1 ratio. If despite adequate ventilation and compressions, the heart rate remains below 60 beats per minute, epinephrine is indicated. The intravenous route is preferred over the endotracheal route and the recommended dose of epinephrine is 0.01–0.03 mg/kg. This can be repeated every 3–5 min until return of spontaneous circulation is achieved. In rare instances, when there is no response to these above measures and in infants who show evidence of significant hypovolemia, volume replacement should be considered.

The vast majority of newborn infants make the transition from fetal to neonatal life without needing intervention beyond supportive measures of providing warmth and stimulation. However, an estimated 10% of neonates do require some help, which mostly takes the form of establishing effective ventilation [1]. Fortunately, the need for cardiopulmonary resuscitation (CPR) with or without the administration of medications is quite rare (approximately 1.2 per 1000 live births) [2]. When this happens however, it is often due to fetal asphyxia in the intrapartum period and has high rates of morbidity and mortality [2,3].

1. Chest compressions

Current Neonatal Resuscitation Program (NRP) guidelines recommend chest compressions for infants who do not respond to effective ventilation and continue to have a heart rate less than 60 beats per minute (bpm) despite at least 30 s of positive pressure ventilation that results in lung inflation. These infants are likely to be asphyxiated and have significant acidosis with consequent myocardial depression. This results in an inability of the heart to adequately pump blood to the lungs and other vital organs. Therefore, there is need to mechanically compress the chest to pump blood to the lungs, brain and heart as well as other vital organs, while simultaneously continuing to ventilate the lungs until the myocardium is oxygenated enough to restore spontaneous function [4].

Given the importance of simultaneously continuing positive pressure ventilation while doing chest compressions, it is preferred that chest compressions be administered from the head of the bed, using the two thumb technique [4]. This allows the compressor to have unrestricted access to the chest and enables proper positioning of the hands in an ergonomically stable manner. Additionally, this position also allows other team members to have room to gain umbilical venous access in the event that medication administration becomes necessary (Fig. 1). Given the importance of ventilation in the return of spontaneous circulation (ROSC), it is essential to coordinate chest compressions with ventilation. While the optimal compression to ventilation ratio for the resuscitation of an asphyxiated newborn has yet to be established [5], current NRP guidelines state that the compression rate should be 90 compressions per minute coordinated with 30 ventilations per minute for a total of 120 events per minute. This is delivered by 3 compressions followed by 1 ventilation every 2 s [4].

2. Epinephrine

Despite adequate ventilation of the lungs and supplementing cardiac output with chest compressions, a small minority of babies (approximately 0.001–0.003% of term and late preterm births) may still have a heart rate below 60 bpm [4]. These newborns may benefit from the use of medications and in some rare instances, volume expansion, given in conjunction with synchronized ventilations and chest compressions.

Epinephrine is the only medication recommended by the International Liaison Committee on Resuscitation for use in newborn resuscitation. It is an endogenous catecholamine with high affinity for α1, β1 and β2 receptors present in cardiac and vascular smooth muscle

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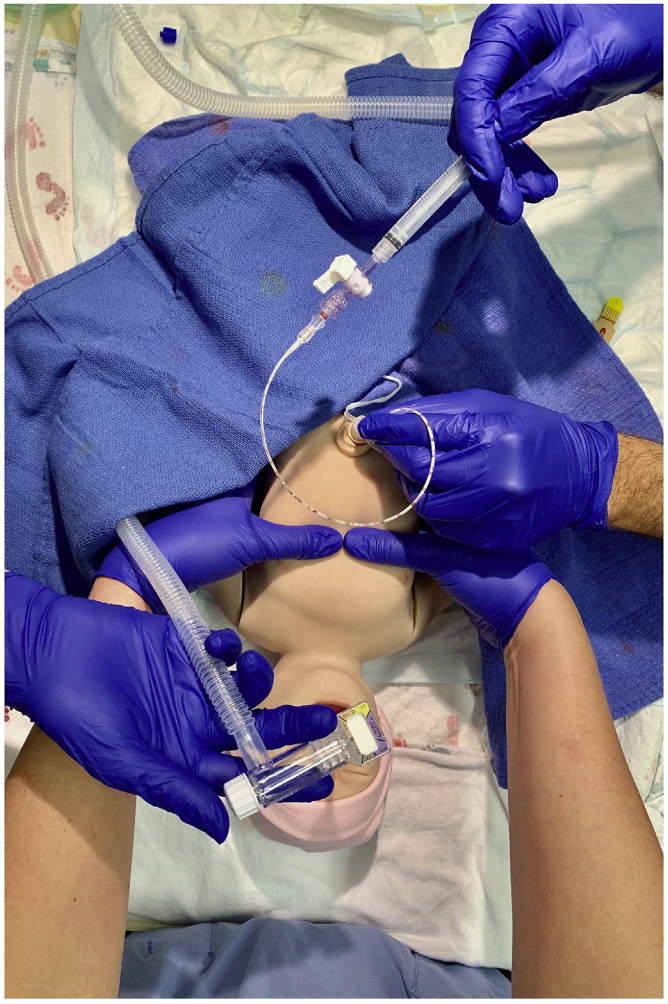

Fig. 1. Team positioning around warmer during extended resuscitation. Note the space available to obtain umbilical venous access while ventilation and head of bed chest compressions are being performed.

[6]. Increased heart rate, conduction velocity and contractility are mediated by its action on β1 and β2 receptors, the sinoatrial node (SA) and the atrioventricular (AV) node. Additionally, through its α1 mediated action, it can affect peripheral vascular resistance by causing peripheral vasoconstriction [7]. In fact, in a canine model of asphyxia, Otto et al. demonstrated no ROSC in canines treated with phenoxybenzamine, a pure α blocker, while there was a 75% rate of ROSC in animals who received the β blocker propranolol [8]. These findings strongly suggest that the efficacy of epinephrine in resumption of spontaneous circulation from asphyxia cardiac arrest is primarily due to α adrenergic receptor stimulation.

In severely asphyxiated newborns, bradycardia and/or cardiac arrests frequently occur as a consequence of underlying hypoxemia, hypercarbia and metabolic acidosis. These infants are commonly very vasodilated with low systemic vascular resistance, which translates into a low aortic diastolic blood pressure (ADBP). Since the coronary perfusion pressure (CPP) is dependent on the ADBP, this can result in insufficient coronary blood flow. Given the α1 mediated effects of epinephrine, it is possible that epinephrine use in these newborns would increase peripheral vascular resistance, thus increasing the CPP and improving coronary blood flow. Interestingly, this theory has not been proven true in a lamb model of neonatal asphyxia, in which epinephrine failed to significantly improve the heart rate, cardiac output and blood pressures in asphyxiated, acidotic lambs [9], creating some controversy regarding this theory.

Table 1
Unique characteristics of transitioning neonatal physiology which affect epinephrine absorption.

1. Fluid filled alveoli which dilute epinephrine
2. High pulmonary vascular resistance may limit pulmonary blood flow
3. Presence of patent ductus arterious (PDA) and patent foramen ovale (PFO), in the presence of high pulmonary pressures may potentiate right-to-left cardiac shunts, enabling blood to bypass the pulmonary circulation
4. Pulmonary vasoconstriction from profound mixed metabolic and respiratory acidosis from asphyxia

As discussed earlier, the causes of bradycardia and ultimately cardiac arrest in newborns differ significantly from the etiologies of adult cardiac arrest, which is commonly characterized by the abrupt cessation of cardiac output following arrhythmias. Adult cardiac arrest usually occurs in a setting of adequately oxygenated blood. Due to the rarity of requirement for medications in neonatal resuscitation, large clinical trials are lacking and current recommendations regarding timing, route and dosing of epinephrine are based largely on animal models or pediatric or adult studies which do not sufficiently reflect the unique features of the transitioning newborn cardiorespiratory system [10] outlined in Table 1.

Prior to any discussion regarding the best route of dosing, it is important to have a basic understanding of the pharmacokinetics of epinephrine. Adult animal data comparing different routes of epinephrine administration in a swine model of traumatic cardiac arrest demonstrated that while the intravenous (IV) route resulted in a higher maximum concentration, the endotracheal (ET) route resulted in variable absorption as compared to the intravenous and intraosseous (IO) routes. However, in this study, the time to ROSC was not substantially different between the three routes employed [11]. While the absorption of endotracheal epinephrine in adult swine was shown to be variable, the bioavailability of ET epinephrine in transitioning neonatal animal models would theoretically be further diminished due to the administration of the ET epinephrine into fluid filled lungs which might additionally hamper absorption into the blood stream. This was elegantly shown in a recent study by Nair et al. in which the investigators compared peak plasma concentrations after ET epinephrine administration in two groups; one group consisting of term transitioning asphyxiated newborn lambs and the other comprising postnatal, post transitioned asphyxiated lambs. They demonstrated lower peak plasma concentrations in the transitioning newborns as compared to the postnatal lambs [12].

Moreover, in a transitioning lamb model of neonatal asphyxia, Vali et al. [13] compared median time to ROSC and peak plasma concentrations between ET doses of epinephrine (0.1 mg/kg) and lower IV and direct right atrial (RA) doses of epinephrine (0.03 mg/kg). The median time to achieve ROSC was significantly longer in the ET epinephrine group as compared to the IV and RA epinephrine groups. That, coupled with the finding of lower peak plasma epinephrine levels in the former group additionally contributes to evidence that ET epinephrine is less efficacious than IV epinephrine.

The superior efficacy of IV epinephrine over ET epinephrine is further established by a retrospective clinical review of all neonates requiring at least one dose of ET epinephrine in the delivery room. It was shown that while 32% of these patients achieved ROSC in response to the first dose of ET epinephrine, of the remaining who failed the initial ET dose, 77% achieved ROSC after IV administration of the drug [1]. It was thus concluded that ET epinephrine is often ineffective. However, in this retrospective study, the dose of ET epinephrine studied was 0.01mg/kg-0.03 mg/kg, which is similar to the IV dose. Given the knowledge derived from animal data with respect to the decreased absorption of ET epinephrine from the fluid filled lungs, this conclusion is unsurprising. Data from some animal studies suggests that higher doses of ET epinephrine (0.05–0.1 mg/kg) may have better potency [14,15]. But the caveat to this is that these animal studies were all

performed in post transitional animals which do not feature all the unique aspects of neonatal transitional physiology that have been discussed previously. Indeed, another recent retrospective clinical study examined the efficacy of higher dose ET epinephrine (0.03 mg/kg to 0.05 mg/kg) as compared to IV epinephrine and demonstrated that both doses of epinephrine when administered via the ET tube often failed to achieve ROSC without subsequent IV epinephrine administration. This could possibly be explained by those factors reviewed in Table 1 which limit the absorption and distribution of the drug [10].

In light of the robust evidence supporting the superiority of the IV route of epinephrine over the ET route, current guidelines strongly recommend establishing IV access and administering IV epinephrine if indicated. In the delivery room, IV access is readily obtained by placing a low lying umbilical venous catheter (UVC). The catheter is inserted between 3 – 5 cm and adequate positioning can be ascertained by obtaining blood return. In the event that IV access is unattainable, it is feasible to attempt IO access considering that there is evidence that the pharmacokinetics of IO and IV epinephrine are comparable [11]. Moreover, a simulation study comparing IO and umbilical catheter placement demonstrated faster IO placement without any difference in technical errors or perceived ease of use [16], suggesting that this may be a good option for inexperienced healthcare professionals attending deliveries. While IV/IO access is being established, it is reasonable to consider a dose of ET epinephrine at 0.05mg/kg-0.1 mg/kg using the 1:10,000 (0.1 mg/ml) preparation [4].

Although IV epinephrine unequivocally has better bioavailability than ET epinephrine, the ideal dose to achieve ROSC while minimizing side effects is as yet uncertain. Since the bioavailability of IV administered epinephrine is 100%, it is plausible that a lower dose may be sufficient to achieve ROSC. This is borne out by animal data which suggests that using higher doses of epinephrine can be detrimental. In an ovine model of asphyxia, Burchfield and colleagues administered graded doses of epinephrine ranging from 0.001mg/kg-0.1 mg/kg. They demonstrated that stroke volume and cardiac output were blunted in those animals administered the high dose of epinephrine (0.1 mg/kg) [17]. Moreover, other animal data demonstrate trends towards decreased cerebral blood flow and higher post resuscitation mortality with high dose epinephrine of 0.2 mg/kg as compared to 0.02 mg/kg [18,19]. Indeed, there is also pediatric clinical data available that furthers the notion that low dose epinephrine (0.01 mg/kg) is equivalent in achieving ROSC as compared to high dose epinephrine (0.1 mg/kg) [20]. Similar findings were demonstrated in another pediatric prospective randomized controlled trial (RCT) conducted by Perondi and colleagues. They found a concerning trend towards increased mortality in the post-resuscitative period, with fewer patients assigned to receive high dose epinephrine (0.1 mg/kg) surviving to hospital discharge [21]. Given all these data evidencing equivalence in the rates of ROSC, coupled with the concerning negative effects associated with high dose epinephrine, current NRP recommendations support the use of lower doses of IV epinephrine in the range of 0.01–0.03 mg/kg. This can be repeated every 3–5 min until ROSC is achieved [4].

3. Practice points

- Epinephrine is indicated if the baby's heart rate remains below 60 bpm despite at least 30 s of effective PPV, preferably through an advanced airway AND
- Another 60 s of chest compressions coordinated with PPV using 100% oxygen.
- IV route is highly recommended over the ET route. Umbilical venous access is preferred. If IV access is unattainable, IO access can be considered.
- While awaiting IV/IO access for administration of epinephrine, it is reasonable to consider an ET dose of epinephrine in the range of 0.05–0.1 mg/kg using the 1:10,000 concentration.
- IV epinephrine dose ranges from 0.01 to 0.03 mg/kg. There is currently no evidence supporting the use of higher IV epinephrine doses.
- The IV dose can be repeated every 3–5 min until ROSC is achieved.

4. Future research directions

Since it is important to minimize interruptions in chest compressions to optimize coronary perfusion pressure and aid ROSC, it is worth investigating the role quantitative end tidal CO2 (ETCO2) monitoring may play during resuscitation. There are three determinants of ETCO2: CO2 production, alveolar ventilation and pulmonary perfusion. Thus, if CO2 production and ventilation are constant, pulmonary perfusion would determine the amount of exhaled CO2 [22]. Since pulmonary perfusion is dependent on cardiac output, it stands to reason that an increase in the amount of ETCO2 would correlate with increased cardiac output and could be used as a surrogate measure of ROSC. This theory has been demonstrated in adults [23]; however it wasn't until very recently that Stine et al., in a retrospective cohort study of resuscitated infants in the pediatric intensive care unit (PICU) and pediatric cardiovascular intensive care unit (CVICU), demonstrated similar findings in an infant age group [22]. Further studies are necessary, not only to corroborate this evidence, but also to evaluate the use of ETCO2 in the delivery room.

5. Volume resuscitation

While effective ventilation is a key step in any resuscitative attempt, adequate circulating volume is another important condition that needs to be fulfilled for successful achievement of ROSC. The need for volume resuscitation in the delivery room is quite rare but has the potential to be lifesaving under certain circumstances. Determining which babies would benefit from volume resuscitation is an important part of the decision making process during an extended resuscitation. Giving additional volume to euvolemic infants in a last ditch effort to improve the heart rate comes with inherent risks, as evidenced by piglet studies, which demonstrated that the use of volume expanders was associated with the development of pulmonary edema without any significant increase in BP [24]. Moreover, there is also evidence that rapid volume administration can impact the coagulation profile, decreasing clot strength [25]. Teams resuscitating preterm infants should be cognizant of the risk of intracranial hemorrhage with rapid volume administration. For these reasons, it is critical to restrict volume administration to those infants who are deemed to be hypovolemic. In instances where there has been evidence of blood loss (Table 2), it is reasonable to assume that these babies may be hypovolemic and candidates to benefit from volume expansion, especially in the presence of signs of shock such as pallor, delayed cap refill and weak pulses [4]. Thus, administration of a volume expander is indicated if the baby does not respond to previous optimized steps of resuscitation AND there is evidence of hypovolemia.

If blood loss or severe fetal anemia is suspected, emergency, noncross matched, type O, Rh negative packed red cells (PRBC) is the fluid of choice for blood loss replacement since it is critical to re-establish oxygen delivery to tissues. The initial recommended dose for any initial volume expansion is 10 ml/kg [4] , given via the umbilical vein or via

Table 2
Indications for volume resuscitation in the delivery room.

1. Acute fetal-maternal hemorrhage
2. Bleeding vasa previa
3. Extensive vaginal bleeding
4. Placental laceration
5. Abruption due to shearing forces, such as a high speed motor vehicular accident
6. Fetal trauma
7. Umbilical cord blood loss

the IO route if IV access is unavailable. Although no clinical trials are available, current guidelines recommend infusing this volume over 5–10 min.

In the event of non availability of O negative PRBC, or if availability will take time, it is reasonable to use an alternative volume expander in the interim period. Evidence shows similar efficacy of crystalloid and colloid solutions [26], however, crystalloids such as 0.9% Saline are generally preferred as they are readily available, cheaper and carry a lower risk of infection [27,28].

6. Sodium bicarbonate

Despite a long history of widespread use, objective evidence that administration of sodium bicarbonate improves outcomes for patients with cardiopulmonary arrest or metabolic acidosis is lacking [29]. In fact, there is concern that use of sodium bicarbonate may compromise coronary perfusion pressure by reducing systemic vascular resistance, producing hypernatremia, hyperosmolarity and excess carbon dioxide, exacerbating central venous acidosis; all potentially contributing towards increased mortality rates [29]. Given these concerns, coupled with the absence of concrete data showing any benefit of use, sodium bicarbonate is NOT recommended for routine use in the delivery room.

7. Naloxone

Naloxone, a specific opiate antagonist, has historically been used in the management of respiratory depression in neonates who may be exposed in utero to opiates. However, a Cochrane meta-analysis of all available relevant clinical trials revealed that although there is some evidence that naloxone may increase alveolar ventilation, there is no strong evidence that naloxone confers any clinically important benefits to newborn infants with respiratory depression [30]. Hence, the current recommendations do NOT support use of naloxone in the delivery room with the preference being to concentrate on providing adequate and effective respiratory support.

In rare but tragic instances, despite optimizing resuscitative measures, the newborn may not respond and remain with an undetectable heart rate. After confirming that the advanced airway continues to remain in place with good chest movement and adequate chest compressions are being administered, ensure that appropriate dosages of epinephrine are being given and there is no evidence of a pneumothorax. If all these conditions are met, NRP guidelines state that absence of a detectable heart rate at 10 minutes is a strong predictor of mortality [4]. It may be reasonable to consider discontinuation of resuscitative measures at this time, but that decision may be dependent on several factors, including but not limited to, gestational age and the family's previously expressed feelings regarding acceptance of morbidity [4]. Hence, these decisions should be made on a case by case basis.

Conflicts of interest

The authors do not have any conflicts of interest.

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