Seminars in Fetal & Neonatal Medicine 18 (2013) 357–361

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Drugs during delivery room resuscitation – What, when and why?

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Keywords:
Adrenaline
Asphyxia
Cardiopulmonary resuscitation
Epinephrine
Neonatal resuscitation
Volume infusion

SUMMARY

Although seldom needed, the short list of medications used for delivery room resuscitation of the newborn includes epinephrine and volume expanders. Naloxone, sodium bicarbonate and the use of other vasopressors are no longer considered helpful during acute resuscitation and are more often administered in the post-resuscitative period under special circumstances. This review examines the existing literature for the two commonly used medications in neonatal resuscitation and identifies the many knowledge gaps requiring further research.

1. Introduction

Medication use during neonatal resuscitation is an uncommon occurrence [1–3]. The majority of newborns require little assistance to stabilize at birth and adapt to extrauterine life. Approximately 10% of newborns require some assistance to begin breathing at birth [4]. If resuscitation steps (particularly effective positive pressure ventilation) are implemented in a skillful and timely manner, most compromised newborns will improve without the need for cardiac compressions or medications [4,5]. Data from cohort studies indicate that medications are required in <0.1% of all live-born deliveries [2,3,6]. Severe fetal acidemia (pH <7.0), malpositioned endotracheal tubes and ineffective ventilator support contribute to the need for the intensive cardiopulmonary support [2]. Thus, it is essential that clinicians optimize positive pressure ventilation (including placement of an endotracheal tube) before resorting to cardiac compressions and medications in the delivery room.

Newborns who fail to respond to optimized ventilation and chest compressions have a high incidence of mortality and long-term morbidity with neurologic deficits if they survive [7,8]. The poor prognosis associated with intensive cardiopulmonary resuscitation (CPR) raises questions as to whether improved CPR methods, including appropriate use of medications specifically tailored to the newborn, could improve outcomes [9].

Due to a lack of rigorous scientific evidence, the role of medications in newborn resuscitation including appropriate dosing, order and route of administration remain controversial. Ethical dilemmas in designing clinical trials for the often unexpected situation of delivery room CPR and the infrequent use of medications for newborns in the delivery room make it difficult to obtain sound clinical evidence. Most delivery room medication recommendations are not based on pediatric or neonatal clinical studies but rather on extrapolations from animal and adult literature. Unfortunately, many of the animal and adult data come from non-perfusing ventricular fibrillation models that are not representative of the cause of cardiovascular collapse in compromised newborns who are frequently asphyxiated. In addition, newborns in the delivery room have unique physiology consisting of fluid-filled alveoli at birth, an open ductus arteriosus and the need to transition from fetal to newborn circulation [10]. These characteristics introduce significant problems in extrapolation of data from animal and adult studies. For preterm infants who are at very high risk of brain injury and intraventricular hemorrhage, the role of resuscitation medications remains extremely controversial [11].

The most frequently used medications during delivery room resuscitation include epinephrine and volume expanders [12]. Naloxone, sodium bicarbonate and other vasopressors are no longer considered part of acute resuscitation and are more often administered in the post-resuscitative period during special circumstances [1,4,13,14]. This review aims to examine the existing literature on the widely used medications in neonatal resuscitation in the delivery room and to identify knowledge gaps requiring further research.

2. Epinephrine

2.1. What is epinephrine?

Epinephrine (adrenaline) is a naturally occurring catecholamine produced by chromaffin cells in the adrenal medulla and stored in

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http://dx.doi.org/10.1016/j.siny.2013.08.001

chromaffin granules. Epinephrine stimulates all four types of adrenergic receptors. Epinephrine causes vasoconstriction via stimulation of α_1 receptors present in vascular smooth muscle. Epinephrine stimulation of α_2 receptors causes presynaptic inhibition of norepinephrine release in the central nervous system and coronary vasoconstriction. Through β_1 receptors, it increases heart rate (chronotropy), conduction velocity (dromotropy), contractility (inotropy) and the rate of myocardial relaxation (lusitropy) [13,15,16]. β_2-Receptor stimulation leads to smooth muscle relaxation and in the myocardium increases contractility, though this effect is minor compared to β_1 effects [13,15–17]. In isolation, stimulation of the various adrenergic receptors can have opposing effects. Epinephrine's effect in vivo depends on the balance between the density of receptor at the target tissue, the receptor's binding affinity for epinephrine, the dose of epinephrine and other local factors [13].

Initially, epinephrine was believed to be effective during CPR due to increased cardiac chronotropy and inotropy through β-adrenergic stimulation [13]. Subsequent studies evaluated the relative contribution of α- and β-mediated effects by using selective adrenergic agonists or by pretreating with selective adrenergic blockade before infusing epinephrine. Redding et al. demonstrated that the pure α-agonist methoxamine was as effective as epinephrine in achieving ROSC during CPR whereas the pure β-agonist, isoproterenol, was no more effective than CPR alone [18]. These findings were confirmed by Otto et al. who used pretreatment with α-adrenergic blockade (phenoxybenzamine) and β-adrenergic blockade (propranolol) before infusing epinephrine [19]. Such studies proved that α-adrenergic stimulation provides the critical action of epinephrine during CPR.

When the heart is hypoxic and depleted of energy substrate to the point that it actually stops pumping, myocardial perfusion with oxygenated blood must be re-established [9]. An acidotic asphyxiated newborn is maximally vasodilated such that the blood pumped by cardiac compressions preferentially flows through the dilated aorta and into the peripheral circulation rather than into the smaller, higher-resistance coronary arteries. Intense epinephrine-mediated peripheral vasoconstriction via α_1 adrenergic stimulation elevates the aortic to right atrial pressure gradient (coronary perfusion pressure) during the relaxation phase of CPR [20]. Once aortic vascular tone is re-established due to the α-adrenergic vasoconstriction of epinephrine, more oxygenated blood enters the coronary arteries to improve myocardial blood flow. Myocardial blood flow facilitates the synthesis of ATP within myocardial mitochondria, thus enhancing cell viability, contractility and ROSC [9]. When myocardial oxygen demand increases, β_2-mediated coronary vasodilation may also contribute to the increased coronary perfusion [13,17,21]. Epinephrine-induced peripheral vasoconstriction also preferentially increases cerebral blood flow and subsequent cerebral oxygen uptake as well as electrographic activity [1,22,23].

2.2. When should epinephrine be administered in the delivery room?

Current neonatal resuscitation guidelines recommend that epinephrine be considered after 30 s of what would appear to be effective ventilation followed by 30 s of co-ordinated chest compressions and ventilations if the heart rate remains <60 beats/min [2]. The preferred route is intravenous and the dose is 0.01–0.03 mg/kg of epinephrine. If there is a significant delay in obtaining intravenous access, epinephrine may be given via the endotracheal tube but this is much less likely to achieve ROSC. A higher dose of 0.05–0.1 mg/kg epinephrine is recommended for endotracheal delivery. Doses may be repeated every 3–5 min.

2.3. Why is this the recommended dosing for epinephrine?

2.3.1. Intravenous epinephrine

Redding et al. demonstrated in an animal ventricular fibrillation model that intravenous epinephrine of 1 mg (0.1 mg/kg in 10 kg dogs), when combined with adequate ventilation and cardiac massage, increased ROSC [1,18]. Human studies following this report did not take into account the weight differences between animals in the study and the average human adult weight and opted still to use 1 mg of epinephrine, an almost 7–10-fold lower dose for an adult based on weight [1,10]. Surprisingly, successful resuscitation was reported even with such a low dose in human adults [24]. This dose was extrapolated to neonatal and pediatric patients with dose range of 0.01–0.03 mg/kg without any clinical data for these populations. Questions soon arose as to whether higher epinephrine doses would be more efficacious. In experimental ventricular fibrillation animal models, escalating dose–response studies showed improved cerebral blood flow, improved left ventricular output, coronary perfusion and increased ROSC with high-dose epinephrine compared to standard-dose epinephrine [20,25]. Adult and pediatric resuscitation protocols began to recommend that if there was no response to standard-dose epinephrine then a 10-fold higher dose subsequently could be administered [10,14,20]. In adult cardiac arrest patients, meta-analysis of randomized control trials showed that high-dose epinephrine increased ROSC but did not affect survival to hospital discharge [25]. In pediatric cardiac arrest populations, two case series with historic controls reported an increase in ROSC with high-dose epinephrine after failing to respond to standard dose with improved neurodevelopmental outcomes in the high-epinephrine group [26,27]. However, this improvement was not confirmed in two randomized controlled trials [28,29]. Perondi et al. conducted a multicenter, randomized, double-blind trial comparing high-dose (0.1 mg/kg) with standard-dose (0.01 mg/kg) epinephrine as rescue therapy for in-hospital cardiac arrest in children after failure of initial standard dose epinephrine [29]. This trial found lower 24 h survival for the high-dose group. It also found markedly reduced survival for the high-dose group when the arrest was precipitated by asphyxia. The two groups did not differ in overall rates of ROSC.

Neonatal specific epinephrine dosing data are sparse. In a neonatal asphyxiated swine model, a blinded randomized controlled trial of high versus standard dose found that high-dose epinephrine was no more effective in improving outcomes at 24 h [30]. Some neonatal animal studies suggest that high-dose epinephrine is harmful. Using a hypoxia-induced bradycardia model in neonatal lambs, Burchfield et al. found that high-dose intravenous epinephrine (0.1 mg/kg) reduced stroke volume and cardiac output [31]. Berg et al. found that animals exposed to high-dose epinephrine during CPR had higher mortality in the immediate post-resuscitation period [30]. In addition, high-dose epinephrine is associated with severe rebound tachycardia and hypertension, resulting in marked increases in myocardial oxygen demand at a time when the myocardial oxygen deficit is substantial [32,33]. The acute hypertension immediately following hypotension during cardiac arrest is important to note as it could increase the risk of intraventricular hemorrhage in premature infants [20,34,35]. There are no neonatal specific clinical data regarding intravenous high-dose epinephrine. Indeed there are no randomized controlled trials in neonates evaluating use of epinephrine at any dose [36].

2.3.2. Endotracheal epinephrine

An optimum dose of endotracheal epinephrine is not yet established for neonates. In animal models, an endotracheal dose