Evidence on Adrenaline Use in Resuscitation and Its Relevance to Newborn Infants: A Non-Systematic Review

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Key Words

Infants · Newborn · Delivery room · Neonatal resuscitation · Adrenaline · Chest compression

Abstract

Aim: Guidelines for newborn resuscitation state that if the heart rate does not increase despite adequate ventilation and chest compressions, adrenaline administration should be considered. However, controversy exists around the safety and effectiveness of adrenaline in newborn resuscitation. The aim of this review was to summarise a selection of the current knowledge about adrenaline during resuscitation and evaluate its relevance to newborn infants. **Methods:** A search in PubMed, Embase, and Google Scholar until September 1, 2015, using search terms including adrenaline/epinephrine, cardiopulmonary resuscitation, death, severe brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia, and adrenaline versus vasopressin/placebo. **Results:** Adult data indicate that adrenaline improves the return of spontaneous circulation (ROSC) but not survival to hospital discharge. Newborn animal studies reported that adrenaline might be needed to achieve ROSC. Intravenous administration (10–30 µg/kg) is recommended; however, if there is no intravenous access, a higher endotracheal dose

(50–100 µg/kg) is needed. The safety and effectiveness of intraosseous adrenaline remain undetermined. Early and frequent dosing does not seem to be beneficial. In fact, negative hemodynamic effects have been observed, especially with doses ≥ 30 µg/kg intravenously. Little is known about adrenaline in birth asphyxia and in preterm infants, but observations indicate that hemodynamics and neurological outcomes may be impaired by adrenaline administration in these conditions. However, a causal relationship between adrenaline administration and outcomes cannot be established from the few available retrospective studies. Alternative vasoconstrictors have been investigated, but the evidence is scarce. **Conclusion:** More research is needed on the benefits and risks of adrenaline in asphyxia-induced bradycardia or cardiac arrest during perinatal transition.

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Introduction

Chest compressions (CC) and adrenaline (epinephrine) are infrequently used in neonatal resuscitation [1–3]. Extensive resuscitation, defined as CC with or without adrenaline administration occurs in 6–10% of very and extremely low birth weight infants [4]. Less is known

about the incidence in term infants, but Perlman and Risser [3] reported a total incidence of CC and/or adrenaline of 0.12% in term and preterm infants. O'Donnell et al. [5] reported in 1998 a mortality rate after cardiopulmonary resuscitation (CPR) including adrenaline administration of 70% in infants ≤ 29 weeks of gestation and 33% in term infants. Overall, 79% of the infants ≤ 29 weeks of gestation either died or survived with severe disability [5]. Although mortality rates have changed over the last couple of decades, particularly in term asphyxiated infants after the introduction of therapeutic hypothermia [6], the rates of mortality and neurodevelopmental impairment remain high [7, 8]. Strategies to optimize CC and medication administration in the delivery room (DR) are needed. Bradycardia immediately after birth is usually the result of inadequate lung aeration [3], profound hypoxemia [9], or (more rarely) hypovolemia from blood loss. Establishing adequate ventilation is therefore the cornerstone intervention in DR resuscitation of bradycardic infants [10]. International resuscitation guidelines recommend CC only if the heart rate remains < 60 /min despite adequate ventilation [10]. If the heart rate does not increase despite effective ventilation and CC administration, adrenaline administration should be considered [10]. However, the use of adrenaline during neonatal resuscitation is largely based on evidence from adult literature [11] and animal studies [12]. In asphyxiated newborn infants with fluid-filled lungs and open vascular shunts, there is limited evidence regarding both the effectiveness and safety of adrenaline [13]. Current controversies surrounding the use of adrenaline in neonatal CPR include (1) the effects of adrenaline versus placebo or no adrenaline [14], (2) optimal dose [15], (3) route of administration [16, 17], (4) timing of administration [18, 19], (5) alternative vasopressors [11], and (6) use in preterm infants [20]. The aim of this review is to summarise a selection of available evidence regarding the use of adrenaline during resuscitation and its relevance to asphyxiated newborn infants.

Methods

A non-systematic literature search was conducted in PubMed, Embase, and Google scholar until September 1, 2015 by three of the authors (M.P., A.L.S., and G.M.S.), using search terms including adrenaline/epinephrine, CPR, death, neurodevelopmental impairment, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, and adrenaline versus vasopressin/placebo. We included studies not restricted to the newborn population. First we limited the broad search to randomized controlled trials. Due to a paucity of identified randomized clinical trials, we included case

series, cohort studies, case-control studies, and even case reports. The evidence base about adrenaline's mechanisms of action is mainly derived from animal studies. Thus, animal studies that we considered relevant were also included. Results were limited to adrenaline use in CPR, and thus excluded adrenaline used for hypotension in the neonatal intensive care unit. Still, the number of references identified through the search was far too large for a systematic evidence evaluation to be completed. We made a selection of references among the identified studies and reports driven by a pragmatic approach that partly reflects our own opinion and expertise in the field of neonatal resuscitation. Since our approach was not systematic, we did not limit our search to specific end points. For the same reason, a systematic evaluation of the quality of the evidence (e.g. AGREE or GRADE) was not performed.

Results

No randomized controlled trials are available investigating mortality and morbidity associated with adrenaline administration during CPR of newborn infants of various gestational ages (GA).

Mechanisms of Action

Human Studies

Adults. Coronary perfusion pressure (CPP) is a predictor of return of spontaneous circulation (ROSC) in human adults [21], and therapies that improve CPP, including adrenaline [22], increase the probability of ROSC [21].

Newborn Term or Preterm Infants. No studies were identified.

Animal Studies

Adult Animals. Through its effect on β -adrenergic receptors, adrenaline increases the conduction velocity and thus the heart rate (chronotropy), as well as contractility (inotropy). In theory, adrenaline is beneficial in CPR due to the combined effects on α - and β -receptors. However, experimental studies in dogs have shown that α -stimulation, but not β -stimulation, is required for successful resuscitation [23, 24]. Little is known about the maturation and distribution of α - and β -adrenergic receptors in term and preterm infants, compared to adults and different animal species [25]. In addition, respiratory [26] and metabolic [27] acidosis may inhibit the favourable haemodynamic responses to adrenaline. There is in fact increasing evidence that the increased myocardial oxygen demand caused by β -adrenergic stimulation can be detrimental when adrenaline is used in a state of persisting hypoxia [28].

Through its effect on α -adrenergic receptors, adrenaline mediates peripheral vasoconstriction while forward flow is generated with CC [29], thus elevating the aortic pressure and CPP in pigs [30]. CPP is determined by the aortic to right atrial pressure gradient during the relaxation ('diastolic') phase of CPR [31, 32]. CPP correlates with myocardial blood flow in dogs [31], and is a positive predictor of ROSC in pigs [30]. Through the same mechanism, adrenaline increases cerebral blood flow in dogs [31]. In addition, α -agonism may counteract CPR-induced collapse of the carotid arteries resulting from elevated intrathoracic pressures, further optimizing cerebral blood flow [31, 33]. Michael et al. [31] demonstrated in dogs with ventricular fibrillation (VF) cardiac arrest that as a result of adrenaline-induced reversal of carotid artery collapse, blood flow increased more to the caudal than rostral regions of the brain, while decreasing blood flow to extracerebral vascular beds.

In adult animals, the effects of adrenaline are not limited to the period of CPR, but may also affect myocardial function after ROSC [34, 35]. Adrenaline, especially in high and repeated doses, has potential adverse effects including (1) prolonged hypertension and tachycardia [35, 36], (2) impairment of the blood brain barrier [37], (3) increased myocardial oxygen demand and oxidative stress [38] with negative post-resuscitation effects on cardiac function [34, 39], and (4) myocardial ischemia and necrosis [40].

Newborn Animals. In neonatal animals, adrenaline might cause imbalance of neurotransmitters and their receptors including γ -aminobutyric acid [41], serotonin [42], acetylcholine [43], and dopamine [44]. However, beneficial effects including increased cerebral blood flow in infant pigs [32] and subsequently cerebral oxygen uptake [32] have also been demonstrated.

Areas of Controversy

Effects of Adrenaline versus Placebo or No Adrenaline Human Studies

Adults. In a double-blind placebo-controlled trial of 534 out-of-hospital cardiac arrests (OHCA), ROSC occurred in 22 (8.4%) patients receiving placebo and 64 (23.5%) receiving adrenaline (OR = 3.4; 95% CI: 2.0–5.6) [14]. Survival to hospital discharge occurred in 5 (1.9%) and 11 (4.0%) patients receiving placebo and adrenaline, respectively (OR = 2.2; 95% CI: 0.7–6.3) [14]. Similarly, Olasveengen et al. [45] randomised 851 patients with OHCA to either intravenous (IV) medication adminis-

tration versus no IV medication administration. Adrenaline was used in the majority of events. Other medications included atropine and amiodarone. Patients with IV medication administration had higher ROSC rates upon hospital admission ($p < 0.001$). However, survival to hospital discharge ($p = 0.61$) and survival with favourable neurological outcome ($p = 0.45$) was similar between the groups [45].

Newborn Term or Preterm Infants. No studies were identified.

Animal Studies

Adult Animals. Using adult rats with asphyxia-induced cardiac arrest, McCaul et al. [46] found that adrenaline administration improved mean aortic pressure, CPP, cerebral perfusion pressure, and ROSC, but with the drawback of increased mortality ($p < 0.05$), hypertension ($p < 0.001$), and tachycardia ($p = 0.004$) compared to saline controls.

Newborn Term Animals. McNamara et al. [11] showed that 14% of asphyxiated piglets with cardiac arrest can achieve ROSC without vasopressors. However, also using asphyxiated piglets with cardiac arrest, Solevåg et al. [47, 48] reported that CC alone did not generate a sufficient diastolic blood pressure as a proxy for CPP. Almost all animals required adrenaline to achieve ROSC [47, 48]. This is further supported by Sobotka et al. [49], who reported that administration of adrenaline was a prerequisite for achieving ROSC in a transitional near-term lamb model of asphyxia-induced bradycardia and hypotension.

Newborn Preterm Animals. No studies were identified. Studies in adult humans, as well as in adult and newborn term animals, suggest that adrenaline improves ROSC both in adult OHCA and in experimental asphyxia-induced cardiac arrest. However, in asphyxia, there might be a trade-off with higher mortality after adrenaline administration.

Optimal Dose

The 2015 International Liaison Committee on Resuscitation (ILCOR) treatment recommendations did not review the use of adrenaline during neonatal resuscitation [10]. However, in 2010 the ILCOR recommended a dose of 10–30 $\mu\text{g/kg}$ IV, and advised against higher IV doses as they might be potentially harmful [50].

Human Studies

Adults. No relevant studies were identified.

Older Children. Perondi et al. [51] randomised 68 children (mean age ~6 years of age) to either 10 versus 100 µg/kg for the 2nd dose of adrenaline after initial failure to one dose of 10 µg/kg. Although ROSC rates were similar, none of the children receiving high-dose adrenaline survived the first 24 h versus a 20.6% survival among those receiving the lower dose. Similarly, Patterson et al. [52] compared 10 versus 100 µg/kg followed by a second dose of 200 µg/kg if needed in paediatric patients with OHCA. No advantage of higher adrenaline doses in terms of ROSC, short- and long-term survival, or neurological outcome were observed. In fact, survival was markedly reduced in the high-dose group when the arrest was precipitated by asphyxia.

Newborn Term or Preterm Infants. No studies were identified.

Animal Studies

Adult Animals. In the rat study by McCaul et al. [46], adrenaline administration resulted in a dose-related reduction in left ventricular end-diastolic diameter ($p < 0.05$), dose-related tachycardia and hypertension, and increased mortality (33% in 10 µg/kg and 72.8% in 30 µg/kg) compared to normal saline (0%) ($p < 0.05$). Serum cardiac troponin-I at 2 h after resuscitation was higher in the animals that received 30 µg/kg adrenaline compared to saline controls.

Newborn Animals. No studies were identified.

These data suggest no advantage of high dose adrenaline, but aggravated hypertension, tachycardia, and increased mortality in asphyxia-induced cardiac arrest. Unfortunately, no randomised studies in newborn infants were identified and are urgently needed.

Route of Administration

ILCOR states that if IV access is not available and adrenaline has to be administered, the endotracheal (ET) route using 50–100 µg/kg should be used. This recommendation is based on a small number of non-neonatal animal studies [53–56] and human case series [5, 16, 57].

Human Studies

Adults. No studies were identified.

Newborn Term or Preterm Infants. An ET adrenaline dose of 50–100 µg/kg might achieve a similar effect as an IV dose of 10 µg/kg [50, 58]. However, clinical observations indicate that only 32% of infants who received the first adrenaline dose via the ET route achieved ROSC [16]. Of the 30 infants who did not achieve ROSC, 77% achieved ROSC after IV adrenaline administration. These

results might be explained by dilution of adrenaline in the fluid-filled alveoli of depressed newborn infants in the DR [59, 60]. Also, elevated pulmonary artery pressures in the presence of a patent ductus arteriosus can potentially result in blood from the right ventricle bypassing the lungs and thus limiting the absorption of adrenaline from the lungs [59, 60].

Case reports indicate that intramuscular administration of adrenaline in newborn infants may cause significant tissue damage at the injection site, even at a 1:10,000 concentration and a dose of 20 µg/kg [61].

Ellemunter et al. [62] reported 27 cases of term ($n = 7$) and preterm ($n = 20$, of which 7 were ≤ 26 weeks of gestation) use of intraosseous access for resuscitation. In addition to catecholamines, infusions included volume expanders, sodium bicarbonate, calcium gluconate, analgesics, sedatives, muscle relaxants, glucose, blood products, and antibiotics. No major complications were noted.

Animals

Adult Animals. In pigs with VF, 100 µg/kg ET adrenaline was compared to 10 µg/kg and control (no adrenaline) [53]. 100 µg/kg resulted in a higher increase in plasma adrenaline levels, but not a higher blood pressure compared to 10 µg/kg adrenaline and control [53]. Roberts et al. [54] demonstrated in dogs that after ET adrenaline administration, the maximum blood concentration of adrenaline was approximately one tenth that achieved with an equal IV dosage.

Newborn Animals. Kleinman et al. [63] compared administration of 10 µg/kg adrenaline into either the femoral vein, the right atrium, or ET during CPR in newborn pigs with VF cardiac arrest. ET administration resulted in lower plasma adrenaline concentrations; however, the number of animals achieving ROSC was similar between all groups.

Mauch et al. [17] demonstrated that 100 µg/kg intramuscular adrenaline resulted in similar ROSC and survival compared to 10 µg/kg IV adrenaline in infant piglets with ropivacaine-induced pulseless electrical activity or asystole.

Simulation Studies

Abe et al. [64] performed a simulation study and reported that the intraosseous access was faster and subjectively easier than the umbilical venous access when inexperienced providers were assessed. However, due to the limited evidence, intraosseous lines are not recommended in newborn resuscitation [7].

In summary, the rate of ROSC seems to be higher with IV versus ET adrenaline administration in newborn infants. Taking into account the unique transitional physiology, there is both clinical and theoretical rationale to suggest that ET adrenaline is less effective than IV administration in DR CPR. Until more data on the safety and effectiveness of intramuscular adrenaline is available, this route of administration is not recommended.

Timing of Administration

Currently, administration of adrenaline is not recommended unless the heart rate remains <60/min despite adequate ventilation and CC [50].

Human Studies

Adults. Warren et al. [18] reviewed almost 21,000 adults with in-hospital cardiac arrests and found that an adrenaline average dosing period (i.e. 'the time between the first adrenaline dose and the resuscitation end point, divided by the total number of adrenaline doses received subsequent to the first adrenaline dose' [18]) of 9–10 min/dose improved survival compared to the recommended 4–5 min/dose [18].

Newborn Term or Preterm Infants. No studies were identified.

Animal studies

Adult Animals. No relevant studies were identified.

Newborn Animals. Linner et al. [19] studied early adrenaline administration in newborn piglets with severe asphyxia and bradycardia. Adrenaline was administered prior to CC, which did not improve ROSC or cerebral regional oxygen saturation when compared to placebo.

These studies suggest that neither early nor frequent adrenaline dosing is beneficial.

Alternative Vasopressors or Adrenaline in Combination with β -Antagonists

Human Studies

Adults. Endogenous vasopressin levels have been found to be higher in successfully resuscitated patients than in patients who died [65]. Thus, it has been suggested that vasopressin might be beneficial in CPR. Vasopressin (40 IU) was superior to adrenaline (1 mg) in OHCA patients with asystole [66]. However, no benefit of adding vasopressin (40 IU) to IV adrenaline (1 mg) during OHCA has been demonstrated in randomized controlled trials [67].

Newborn Term or Preterm Infants. No studies were identified.

Animals

Adult Animals. Vasopressin is a potent vasoconstrictor and might be used as an alternative to or addition to adrenaline during CPR [11, 68, 69]. Studies in adult pigs and rats have reported that either β -receptor antagonism (e.g. esmolol [34]) or selective α -agonism (e.g. phenylephrine [29, 34]) potentially reduce the detrimental side effects of adrenaline.

In rats with VF, 30 μ g/kg adrenaline and 300 μ g/kg phenylephrine had similar haemodynamic effects during CPR; however, post-ROSC myocardial dysfunction was increased and the duration of survival after ROSC was decreased after adrenaline compared to phenylephrine administration [34]. 30 μ g/kg adrenaline combined with 300 μ g/kg esmolol resulted in similar effects as phenylephrine, with improved myocardial function and survival after ROSC compared to adrenaline alone [34].

Newborn Animals. A continuous infusion of phenylephrine (40¹⁵ or 20⁷⁰ μ g/kg/min) had similar effects as adrenaline in infant pigs [15] and dogs [70] with VF cardiac arrest.

No clinical studies are available about vasopressin, esmolol, or phenylephrine in paediatric or neonatal CPR. Thus, alternative vasopressors to adrenaline cannot be recommended in DR CPR.

Preterm Infants

Studies about the benefits and risks of adrenaline during DR CPR of preterm infants are completely lacking. However, large cohort studies have shown that extensive DR CPR is associated with intraventricular haemorrhage grades 3–4 in extremely preterm infants [1, 2, 71] potentially caused by blood pressure fluctuations aggravated by adrenaline administration [72]. Also, there is a theoretical possibility that adrenaline, through its vasoconstrictive effects, may cause major organ injury including renal failure and NEC in vulnerable individuals [73, 74].

Frontanes et al. [71] compared the outcomes of 80 very low birth weight infants (i.e. <1,500 g) who required extensive DR CPR to 221 GA- and birth weight-matched infants without CPR. Not surprisingly, infants receiving CPR interventions had significantly lower survival (26 vs. 43%, $p < 0.01$) and survival without brain injury (17 vs. 32%, $p = 0.011$), as well as higher rates of respiratory distress syndrome ($p < 0.01$) and NEC (20 vs. 9%, $p = 0.018$) [71].

In 13,758 extremely preterm infants (GA 22 + 0 to 27 + 6 weeks), Handley et al. [1] found that DR CPR was associated with early-onset sepsis, intraventricular haemorrhage grades 3–4, postnatal steroids, and death before hospital discharge, but not with death in the first 12 h of life, pneu-

mothorax, patent ductus arteriosus, cystic periventricular leukomalacia, NEC, or bronchopulmonary dysplasia.

Extensive DR CPR is therefore associated with lower survival rates with or without neurological impairment, especially in low birth weight infants. However, limitations of most of the retrospective studies include that they do not distinguish between DR CPR with CC alone or CC + adrenaline, or between infants receiving CPR interventions and those who truly need CC and/or adrenaline [3]. Another very important limitation is that, if used correctly, adrenaline is given to the most compromised infants who are likely to have the worst outcomes irrespective of the adrenaline administration.

Knowledge Gaps

Current knowledge on the use of adrenaline in newborn infants is limited to retrospective studies, as well as extrapolations from animals and adult humans. Most animal studies of newborn resuscitation including adrenaline have been performed in post-transitional animals. The unique transitional physiology with fluid-filled lungs and elevated pulmonary vascular pressure, as well as open fetal shunts, make studies in animals during the perinatal transition warranted. There are significant physiological differences in different GA groups, and therapies including adrenaline are likely to have GA-specific effects and side effects. Guidelines for neonatal resuscitation do not differentiate between different GA groups for CC and adrenaline. The knowledge about physiological effects with resulting risks and benefits in preterm infants is completely lacking. Performing randomised controlled trials remains difficult, mainly due to the low incidence of infants requiring DR CC with or without adrenaline, as well as ethical concerns. The vast majority of studies in animals and humans were in VF arrest, not asphyxia. Currently, there is a lack of data about benefits and risks, dose, and timing of adrenaline administration in asphyxia-induced bradycardia. Data to assess the interactions of adrenaline with α - and β -adrenergic receptors during or after CC in different GA is needed. Lastly studies should examine potential alternative vasoconstrictor drugs to be administered during neonatal CPR.

Conclusion

VF animal models have shown that adrenaline increases aortic pressure, coronary perfusion, and cerebral perfusion pressure. However, these favourable effects might be

attenuated and/or counterbalanced in newborn infants due to (1) asphyxia with a combined respiratory and metabolic acidosis, (2) potentially different expression and sensitivity of subtypes of adrenergic receptors, and (3) vulnerability of preterm infants to fluctuations in blood pressure. In newborns, only retrospective data is available about the outcomes after adrenaline administration during CPR. A causal relationship between CPR with or without adrenaline and outcomes cannot be established in the retrospective studies, but extensive CPR with or without adrenaline administration seems to be associated with increased risk of intraventricular haemorrhage in preterm infants. In compromised infants of all gestations, care should be taken to optimize the assisted ventilation before initiating CC and/or administering adrenaline. More research is needed in appropriate animal models and if possible in clinical trials. While acknowledging the ethical challenges of performing CPR research in newborn infants, as well as the infrequent occurrence of DR CPR interventions, we propose the following important research questions to be further investigated:

- 1 In newborn infants requiring extensive resuscitation, what is the relationship between the extent of resuscitation and the survival rate and long-term outcomes of survivors?
- 2 In asphyxiated newborn infants, does adrenaline administration prior to initiation of CC reduce time to ROSC compared to adrenaline administration after 30 s of CC?
- 3 In asphyxiated newborn infants, do other vasopressors (e.g. vasopressin) during DR CPR improve the outcomes including time to ROSC, mortality, and/or morbidity compared to adrenaline?
- 4 In preterm infants, does adrenaline administration during DR CPR affect the outcome including time to ROSC, mortality, and/or morbidity compared to placebo?

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Disclosure Statement

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