APS European Society for Paediatric Research SPR Society for Pediatric Research

COMMENT

Is epinephrine effective during neonatal resuscitation?

Deepika Sankaran[1,2]✉, Eleanor J. Molloy[3] and Satyan Lakshminrusimha[1]

Pediatric Research (2023) 93:466–468; https://doi.org/10.1038/s41390-022-02411-2

Epinephrine (adrenaline) is the only medication recommended by the International Liaison Committee On Resuscitation (ILCOR) during resuscitation in newborns with persistent bradycardia or asystole.[1] However, there are no randomized clinical trials investigating epinephrine use in the delivery room owing to its infrequent use during resuscitation (~0.05–0.06% of live births),[2] difficulty in predicting its need and ethical challenges. Retrospective studies and large multicenter observational studies and registries are providing valuable clinical data on survival and long-term neurodevelopmental outcomes.

Translational studies in animal models have significantly contributed to the evidence supporting epinephrine use in neonatal resuscitation. However, differences in animal species, age and related physiological changes, variations in induction of bradycardia and cardiac arrest and timing and route of epinephrine have led to differences in outcomes and results (Fig. 1). In a recent issue of the journal *Pediatric Research* Andersen et al. presented novel data from their randomized placebo-controlled trial evaluating epinephrine use in porcine neonatal cardiac arrest with a 6-h follow-up and magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) of the brain.[3] Epinephrine (0.01 mg/kg/dose) administered at 1 min after the onset of resuscitation resulted in a higher incidence of return of spontaneous circulation (ROSC) compared to placebo (epinephrine 10/13 vs placebo 4/12, RR 2.31; 95% CI: 1.09–5.77, $p = 0.047$). However, the authors observed no difference between the groups in median time to ROSC from initiation of resuscitation (epinephrine: 120 (113–211) vs placebo 153 (116–503) s, $p = 0.66$), and 6-h survival (7/13 vs 3/12, $p = 0.23$), or lactate to N-acetyl aspartate (Lac/NAA) ratio by MRS and composite outcome of death or abnormal MRI/MRS. The authors comment, "newborn animal models of cardiac arrest have failed to produce convincing evidence to support the use of epinephrine in neonatal resuscitation". In this commentary, we review existing data on the efficacy of epinephrine during neonatal resuscitation.

DATA FROM CLINICAL STUDIES AND ANIMAL STUDIES

Retrospective clinical studies[2,4] show approximately 76% ROSC following epinephrine in the delivery room but only 44% survival to NICU discharge. Such sparse human evidence is of very low certainty demonstrating the limits of our current knowledge of epinephrine in neonatal resuscitation. In contrast, several studies in newly born lamb models show a high rate of ROSC with epinephrine.[5–7] These models induced asphyxia by umbilical cord compression, a clinically relevant cause of birth asphyxia, compared to endotracheal tube occlusion in postnatal piglets (Fig. 1). Newly born lambs have lung fluid that dilutes endotracheal epinephrine reducing the efficacy of first dose of epinephrine by endotracheal route (55%) as compared to umbilical venous catheter (UVC; 82%).[5] In 12-h-old piglets, the lungs are no longer fluid-filled and are ventilated with air as the cardiopulmonary transition has already occurred prior to cardiac arrest. In addition, an open ductus arteriosus limits the build-up of diastolic blood pressure, a key determinant of coronary perfusion pressure during chest compressions (CC). In spite of this limitation, neonatal lambs in cardiac arrest have a high incidence of ROSC with very low diastolic pressures (<10 mm Hg) in contrast to studies from postnatal animal models[3] and in children.

VARIATIONS IN STUDY DESIGN

In addition to these physiological differences in species and age, variations in study design make a comparison between neonatal animal studies difficult. Andersen et al. defined cardiac arrest as mean blood pressure <20 mm Hg and heart rate (HR) < 60 bpm, and resuscitation was initiated 5 min after the above criteria were met (leading to asystole or pulseless electrical activity). In contrast to stricter definitions based on duration of asystole (HR = 0) used in previous studies,[6] it is possible that the definition used may lead to piglets with varying degrees of asphyxia included in the current study.

OPTIMIZING CHEST COMPRESSIONS

The Textbook of American Academy of Pediatrics-Neonatal Resuscitation Program (AAP-NRP) currently recommends synchronous 3:1 compression-to-ventilation ratio with approximately 90 CC and 30 breaths per min. Asynchronous CC and ventilation, as in the Andersen et al. study, is a deviation from current guidelines which they have acknowledged in their limitations. However, in animal models, asynchronous CC provides a higher rate (~120/min vs. 90/min with synchronous 3:1 compression-to-ventilation ratio) with increased blood flow and oxygen delivery to the brain.

The piglet model has an advantage with thoracic shape amenable to anteroposterior CC (Fig. 1) and is more suitable to study CC depth.[8] Bruckner et al. recently reported higher incidence and shorter time to ROSC with CC at 33–40% of anteroposterior thoracic diameter (0% ROSC with 12.5% depth,

[1]Department of Pediatrics, University of California, Davis, Sacramento, CA, USA. [2]Adventist Health and Rideout Hospital, Marysville, CA, USA. [3]Discipline of Paediatrics, Trinity College Dublin, the University of Dublin, Trinity Research in Childhood Centre (TRICC) and Trinity Translational Medicine Institute (TTMI), Trinity College Dublin, Dublin, Ireland. ✉email: dsankaran@ucdavis.edu

Received: 8 August 2022 Revised: 18 October 2022 Accepted: 17 November 2022
Published online: 12 December 2022

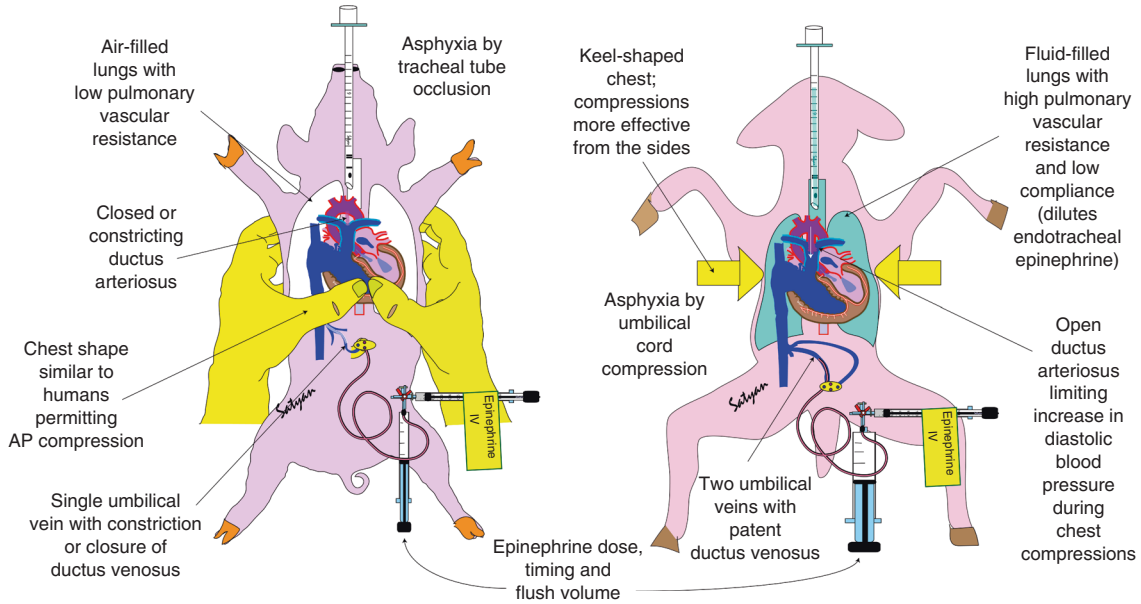

Fig. 1 Animal models for neonatal resuscitation. Differences between postnatal piglet (left) and perinatal lamb (right) models of asphyxial cardiac arrest.

75% with 1/4 depth, 88% with 1/3 and 2/5th depth).[8] The lamb chest is "keel-shaped" resulting in CC administered from the side with the lamb in a decubitus position.

TIMING OF EPINEPHRINE ADMINISTRATION

In clinical situations, every attempt should be made to deliver intravenous or intraosseous epinephrine as soon as possible if positive pressure ventilation (PPV) and CC are not effective in restoring HR.[5] Administering an epinephrine dose at 1 min after the onset of PPV and 30 s of CC is ideal but may be impractical in the delivery room as 5.4 ± 2.2 min are needed to place an emergent UVC and administer the first dose of epinephrine.[2] In animal studies, early epinephrine may potentially lead to unnecessary use in some animals who might have recovered spontaneously. Delaying epinephrine until 4–6 min of resuscitation is associated with ROSC prior to epinephrine in lambs,[6,7] similar to clinical studies where only 40% of term infants (≥36 weeks) receiving CC for >1 min receive epinephrine.[9,10] Optimal interval between epinephrine doses warrants further study.

ROUTE OF EPINEPHRINE ADMINISTRATION

Intravenous (UVC inserted 2–4 cm below the skin) and intraosseous routes are effective in lamb models of neonatal cardiac arrest.[3,5,11] Andersen et al. do not specify the depth of UVC placement and in the absence of plasma epinephrine concentrations, one cannot be certain that piglets that failed to achieve ROSC received epinephrine in their general circulation. In addition, the ductus venosus may begin to close, thus affecting the delivery of epinephrine through a low UVC in a 12-h-old piglet.

FLUSH VOLUME

Andersen et al. acknowledged the use of 1-ml flush volume following UVC epinephrine may not have been adequate to propel epinephrine to the right atrium during CC.[3] Based on studies in lambs with higher flush volume,[6] AAP-NRP now recommends a 3-ml flush following intravenous and intraosseous epinephrine.

EPINEPHRINE DOSE

A 0.01 mg/kg dose of epinephrine was used by Andersen et al. for initial and repeat doses. We have previously shown a higher incidence of ROSC and higher plasma epinephrine concentrations with a larger dose of epinephrine (0.02 and 0.03 mg/kg). Recent studies with the use of 0.02 mg/kg of UVC epinephrine resulted in successful ROSC in 7/8 (87.5%) lambs with peak plasma epinephrine concentrations of 333 ± 79 ng/mL. Although plasma epinephrine concentrations are not good predictors of ROSC (233 ± 138 vs 505 ± 556 ng/mL, $p = 0.11$, in lambs that achieved ROSC vs no ROSC after 0.01 mg/kg epinephrine dose), they could still help determine if epinephrine entered the general circulation.[6] Based on our current data from lambs, we concur with AAP-NRP and suggest 0.02 mg/kg as the initial dose of intravenous epinephrine.[12]

It is possible that the lack of difference in survival and brain imaging noted by Andersen et al. is due to the severe asphyxia in this model. There is no published evidence that epinephrine administration is associated with changes in MRS/MRI, although it may be associated with an increase in cerebral blood flow. Although an Apgar score of 0 at 10 min was associated universally with poor outcomes in the pre-hypothermia era, Laptook et al. showed better outcomes in 208 infants in a secondary analysis of neonates enrolled in cooling trials.[13] Death or disability occurred in 76% (19/25) of infants with a 10-min Apgar score of 0, death occurred in 48%, and among 13 survivors, 7 (54%) had moderate-to-severe disability, and 6 (46%) did not, and in fact had a Mental Developmental Index of 87 ± 9 (range: 73–100).[13] A systematic review evaluating newborns requiring resuscitation beyond 10 min reported that 10.8% of the newborns survived without moderate-to-severe impairment. Further study of neurological outcomes after epinephrine is vital due to the worse neurological outcomes reported in adult out-of-hospital arrest and pediatric resuscitation.[14]

Andersen et al. provide valuable data comparing epinephrine and placebo during neonatal resuscitation. We applaud the authors for moving beyond short-term outcomes in preclinical studies and evaluating brain MRI/MRS changes. However, based on the limitations mentioned in this commentary, in our opinion, these findings should not influence change in the current guidelines from ILCOR and AAP-NRP. Animal studies with longer

(3–7 day) follow-ups with MRI/MRS or brain histology studies are needed.[15] Large multicenter observational studies and registries with long-term follow-ups are warranted to assess the impact of epinephrine during resuscitation.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Wyckoff, M. H., Weiner, G. M. & Neonatal Life Support Collaborators. 2020 International Consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Pediatrics* **147**, e2020038505C (2021).
2. Halling, C., Sparks, J. E., Christie, L. & Wyckoff, M. H. Efficacy of intravenous and endotracheal epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *J. Pediatr.* **185**, 232–236 (2017).
3. Andersen, H. B. et al. Epinephrine vs placebo in neonatal resuscitation: ROSC and brain MRS/MRI in term piglets. *Pediatr. Res.* (2022).
4. Barber, C. A. & Wyckoff, M. H. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* **118**, 1028–1034 (2006).
5. Vali, P. et al. Evaluation of timing and route of epinephrine in a neonatal model of asphyxial arrest. *J. Am. Heart Assoc.* **6**, e004402 (2017).
6. Sankaran, D. et al. Effect of a larger flush volume on bioavailability and efficacy of umbilical venous epinephrine during neonatal resuscitation in ovine asphyxial arrest. *Children (Basel)* **8**, 464 (2021).
7. Sankaran, D. et al. Randomised trial of epinephrine dose and flush volume in term newborn lambs. *Arch. Dis. Child Fetal Neonatal Ed.* **106**, 578–583 (2021).
8. Bruckner, M. et al. Assessment of optimal chest compression depth during neonatal cardiopulmonary resuscitation: a randomised controlled animal trial. *Arch. Dis. Child Fetal Neonatal Ed.* **107**, 262–268 (2022).
9. Foglia, E. E. et al. Duration of resuscitation at birth, mortality, and neurodevelopment: a systematic review. *Pediatrics* **146**, e20201449 (2020).
10. Foglia, E. E. et al. Survival after delivery room cardiopulmonary resuscitation: a national registry study. *Resuscitation* **152**, 177–183 (2020).
11. Roberts, C. T. et al. Comparison of intraosseous and intravenous epinephrine administration during resuscitation of asphyxiated newborn lambs. *Arch. Dis. Child Fetal Neonatal Ed.* **107**, 311–316 (2022).
12. Vali, P., Weiner, G. M., Sankaran, D. & Lakshminrusimha, S. What is the optimal initial dose of epinephrine during neonatal resuscitation in the delivery room? *J. Perinatol.* **41**, 1769–1773 (2021).
13. Laptook, A. R. et al. Outcome of term infants using Apgar scores at 10 min following hypoxic-ischemic encephalopathy. *Pediatrics* **124**, 1619–1626 (2009).
14. Hagihara, A. et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA* **307**, 1161–1168 (2012).
15. Mike, J. K. et al. An ovine model of perinatal hypoxic-ischemic encephalopathy with resultant motor impairment aimed at low resource settings. *Dev. Neurosci.* (2022).

AUTHOR CONTRIBUTIONS

D.S. and S.L. made substantial contributions to the conception and design, data acquisition, and interpretation of data and drafting the manuscript. E.J.M. made substantial contributions to the concept, design, editing and revising the manuscript. All authors critically revised and approved the final version for publication.

FUNDING

This work was supported in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) 5 R01 HD072929 09 (S.L.), and research grant from the American Academy of Pediatrics-Neonatal Resuscitation Program (D.S.), and Children's Miracle Network at UC Davis Pediatrics (D.S.).

COMPETING INTERESTS

The named authors have no conflict of interest, financial or otherwise. S.L. is a member of the American Academy of Pediatrics (AAP), Neonatal Resuscitation Steering Committee (NRP). Views expressed in this manuscript are those of authors and do not reflect the official position of AAP/NRP.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Deepika Sankaran.