www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2013;2(2):e020228
doi: 10.7363/020228

Review

Adrenaline in neonatal resuscitation: are there knowledge gaps?

Athanasios Chalkias[1], Nicoletta Iacovidou[2], Angeliki Syggelou[1], Theodoros Xanthos[1]

[1]National and Kapodistrian University of Athens, Medical School, MSc "Cardiopulmonary Resuscitation", Athens, Greece

[2]2nd Department of Obstetrics and Gynecology, Neonatal Division, National and Kapodistrian, University of Athens, Medical School, Greece

Proceedings

Proceedings of the 9th International Workshop on Neonatology · Cagliari (Italy) · October 23rd-26th, 2013 · *Learned lessons, changing practice and cutting-edge research*

Abstract

Despite the widespread use of adrenaline in adult cardiopulmonary resuscitation, the main concern in using this drug in neonates is the lack of evidence. At present, there are very few reliable human and animal data to justify the use of adrenaline in neonatal resuscitation and significant knowledge gaps exist, which necessitate further research.

Keywords

Adrenaline, neonates, resuscitation, knowledge gaps.

Corresponding author

Theodoros Xanthos, National and Kapodistrian University of Athens, Medical School, MSc "Cardiopulmonary Resuscitation", Hospital "Henry Dunant", 107 Mesogion Av., 115 26, Athens, Greece; tel.: +30 210 6972144; fax: +30 210 6972396; email: theodorosxanthos@yahoo.com.

How to cite

Chalkias A, Iacovidou N, Syggelou A, Xanthos T. Adrenaline in neonatal resuscitation: are there knowledge gaps? J Pediatr Neonat Individual Med. 2013;2(2):e020228. doi: 10.7363/020228.

Background

More than 400,000 infants born in the United States annually need some assistance to begin breathing at birth, while approximately 1% of live births requires extensive resuscitation [1]. Despite the widespread use of drugs during adult cardiopulmonary resuscitation (CPR), drugs are rarely used in neonatal resuscitation. In neonates, bradycardia is usually caused by inadequate lung inflation or hypoxia and the use of adrenaline is considered only if the heart rate remains less than 60 min^{-1} despite adequate ventilation and initiation of chest compressions [2].

The main concern in using adrenaline is the lack of human data, as most evidence comes from animal studies. Nevertheless, adrenaline is the best established of the drugs used in neonatal resuscitation and current guidelines recommend a dose of 0.01-0.03 mg/kg as soon as possible when optimal CPR fails to increase the heart rate. Even though adrenaline has been used in neonatal resuscitation for long, its dose, order and route of administration have been issues of debate among neonatologists and resuscitation experts [3].

Appropriate dose

Although more data now exist from animal and human studies of hypoxic arrest, evidence for the most appropriate dose to use is lacking for all age groups [4]. Of note, the frequency of dosing has been varying four-fold across different populations [5-7], raising the possibility of adrenaline overdose with serious potential side effects [8], However, the most usually used dose in animals studies of neonatal resuscitation is 0.1-0.3 mg/kg and has been extrapolated as the currently recommended range [2]. As a result, the appropriate dose of adrenaline in human neonatal CPR remains unknown and what needs further clarification is whether the dose should be different in term and preterm babies.

Administration route

Adrenaline is preferably administered intravenously *via* an umbilical venous catheter. The tracheal route is not recommended but if it is used, increased doses of 50-100 μg kg^{-1} are required. However, neither the safety nor the efficacy of these higher tracheal doses has been extensively studied. Several authors have shown that during cardiac arrest endotracheal adrenaline is absorbed slowly and erratically, while it is not as effective as when administered intravenously, even in larger doses [8, 9-12]. In addition, tracheal administration may result in low-quality CPR. In a case report of a term infant requiring resuscitation, there was a false-positive color change on the colorimetric carbon dioxide device as a result of administration of adrenaline via the endotracheal tube [13]. Given the lack of supportive data for endotracheal adrenaline, the IV route should be used as soon as venous access is established.

Intraosseous access is another alternative, when intravascular access is not possible. Although intraosseous access is rarely needed in neonates because of the possibility for intravenous catheter placement, insertion of an intraosseous needle has been described in neonates with encouraging results. In a recent study, Rajani et al. compared time to placement, errors in placement, and perceived ease of use for umbilical venous catheters and intraosseous needles in a simulated delivery room and reported that intraosseous needle placement can be performed more quickly without any difference in technical error rate or perceived ease of use [14]. Furthermore, the recently updated American College of Critical Care Medicine guidelines for the management of newborns and children with septic shock emphasize the role of intraosseous access in the management of neonatal septic shock [15]. Intraosseous access is most likely required in out-of-hospital settings and in hospitalized infants without intravenous access [16]. At present, the currently recommended route for adrenaline administration is *via* an umbilical venous catheter with the endotracheal route recommended when there is no alternative. Larger studies are needed to identify whether the intraosseous access is as effective as the umbilical vein in terms of skill, time and whether there is any difference in retention of the 2 procedures. Even if data, from pediatric and adult studies shows that adrenaline dose is the same for intraosseous and intravenous administration, these should be confirmed in the neonatal population.

Post-resuscitation period and outcome

After return of spontaneous circulation, the patients pass through the 'Clashing Rocks' of post-cardiac arrest syndrome. Temperature control and optimization of ventilation and hemodynamics remain the gold-standards for increasing the

possibilities for optimal development of the resuscitated neonates [3].

During ischemia, energy stores of the brain are depleted and lactate and hydrogen ion accumulate, while upon reperfusion, injury is secondary to excitotoxicity, calcium accumulation, protease activation, and formation of reactive oxygen and nitrogen species [17]. Although adrenaline induces pulmonary ventilation/perfusion defects during CPR, it also increases the myocardial lactate content, and decreases the myocardial ATP content in adult cardiac arrest victims [18], evidence on neonatal post-resuscitation myocardial stunning is lacking and further research is necessary.

Although a significant number of very-low-birth-infants receiving adrenaline in the delivery room survive [19-21], a study on the effect of continuous adrenaline infusion in extremely low birth weight infants, reported that all infants which received adrenaline at a dose > 1.0 mcg/kg/hour intravenously died; the authors concluded that extreme caution should be taken when using adrenaline infusion in these high-risk infants [22]. In addition, the requirement of adrenaline in the delivery room during resuscitation may be associated to worst outcomes and decreased survival without severe brain injury [23]. A randomized, blinded trial of high-dose *versus* standard dose adrenaline in asphyxiated neonatal piglets reported no advantage in terms of survival at 24 hours and was associated with tachycardia and hypertension which increase the risk of intraventricular hemorrhage in preterm infants [11].

Furthermore, hypoxic brain injury during neonatal development can lead to neuronal damage and produce learning and cognitive impairments. Anju et al. reported that the administration of exogenous adrenaline in hypoxic fetuses with increased levels of labor-induced endogenous catecholamines can cause a hyperactivity of excitatory stimulus, which may affect the various neurotransmitter levels thereby declining body's adaptations to overcome hypoxia [24]. Raveendran et al. recently reported that resuscitation with adrenaline and 100% oxygen resulted in increased apoptosis in the cerebral cortex, cerebellum, brain stem, and striatum of hypoxic neonatal rats and hypoxic rats, increasing thus, the possibilities for spatial memory and learning deficits during development [25]. Also, in a recent study evaluating neonatal hypoxic insult mediated cholinergic disturbances, adrenaline did not show reversal in altered muscarinic receptors or enzymes in acetylcholine metabolic pathway. In addition, it decreased the uptake of glutamate in the brain causing persistent activation of glutamate receptors, which is capable of causing cholinergic dysfunction [26]. Even though adrenaline is clinically administrated to enhance the contractile state of the heart and to avoid hypoxia mediated complications, its inefficiency in balancing the homeostasis of cholinergic system while encountering neonatal hypoxia limits its therapeutic application. The effects of adrenaline on post-cardiac arrest syndrome are unknown. There is evidence that adrenaline adversely affects all components of the syndrome, inhibiting post-arrest neonatal development and decreasing the survival rates of survivors. As a result, whether adrenaline has detrimental effects in the ischemia/reperfusion injury, in the post arrest myocardial dysfunction and in the post-arrest brain syndrome, are still a matter of debate.

Conclusions

At present, there are very few reliable human and animal data to justify the use of adrenaline in neonatal resuscitation. Significant knowledge gaps exist which necessitate immediate research in the field.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Raghuveer TS, Cox AJ. Neonatal resuscitation: an update. Am Fam Physician. 2011;83(8):911-8.
2. Richmond S, Wyllie J. European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth. Resuscitation. 2010;81(10):1389-99.
3. Iacovidou N, Vasileiou PV, Papalois A, Syggelou A, Bassareo PP, Xanthos T. Drugs in newborn resuscitation: the more we learn the least we use. Curr Med Chem. 2012;19(27):4606-16.
4. Wyckoff MH, Perlman JM. Use of high-dose epinephrine and sodium bicarbonate during neonatal resuscitation: is there proven benefit? Clin Perinatol. 2006;33(1):141-51.
5. Perlman JM, Risser R. Cardiopulmonary resuscitation in the delivery room: associated clinical events. Arch Pediatr Adolesc Med. 1995;149(1):20-5.
6. O'Donnell AI, Gray PH, Rogers YM. Mortality and neurodevelopmental outcome for infants receiving adrenaline in neonatal resuscitation. J Paediatr Child Health. 1998;34(6):551-6.

7. Jankov RP, Asztalos EV, Skidmore MB. Favourable outcomes following delivery room cardiopulmonary resuscitation of infants 750 g at birth. J Paediatr Child Health. 2000;36(1):19-22.
8. Wykoff MH, Wyllie J. Endotracheal delivery of medications during neonatal resuscitation. Clin Perinatol. 2006;33(1):153-60.
9. Orlowski JP, Gallagher JM, Porembka DT. Endotracheal epinephrine is unreliable. Resuscitation. 1990;19(2):103-13.
10. Crespo SG, Schoffstall JM, Fuhs LR, Sivey WM. Comparison of two doses of endotracheal epinephrine in a cardiac arrest model. Ann Emerg Med. 1991;20(3):230-4.
11. Wyllie J, Niermeyer S. The role of resuscitation drugs and placental transfusion in the delivery room management of newborn infants. Semin Fetal Neonatal Med. 2008;13(6):416-23.
12. Barber CA, Wykoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. Pediatrics. 2006;118(3):1028-34.
13. Hughes SM, Blake BL, Woods SL, Lehmann CU. False-positive results on colorimetric carbon dioxide analysis in neonatal resuscitation: potential for serious patient harm. J Perinatol. 2007;27(12):800-1.
14. Rajani AK, Chitkara R, Oehlert J, Halamek LP. Comparison of umbilical venous and intraosseous access during simulated neonatal resuscitation. Pediatrics. 2011;128(4):e954-8.
15. Kissoon N, Orr RA, Carcillo JA. Updated American College of Critical Care Medicine – pediatric advanced life support guidelines for management of pediatric and neonatal septic shock: relevance to the emergency care clinician. Pediatr Emerg Care. 2010;26(11):867-9.
16. Engle WA. Intraosseous access for administration of medications in neonates. Clin Perinatol. 2006;33(1):161-8, ix.
17. Manole MD, Kochanek PM, Fink EL, Clark RS. Postcardiac arrest syndrome: focus on the brain. Curr Opin Pediatr. 2009;21(6):745-50.
18. Chalkias A, Xanthos T. Pathophysiology and pathogenesis of post-resuscitation myocardial stunning. Heart Fail Rev. 2012;17(1):117-28.
19. Finer NN, Tarin T, Vaucher YE, Barrington K, Bejar R. Intact survival in extremely low birth weight infants after delivery room resuscitation. Pediatrics. 1999;104(4):e40.
20. Shah PS, Shah P, Tai KFY. Chest compression and/or epinephrine at birth for preterm infants <32 weeks gestational age: matched cohort study of neonatal outcomes. J Perinatol. 2009;29(10): 693-7.
21. Finer NN, Horbar JD, Carpenter JH. Cardiopulmonary resuscitation in the very low birth weight infant: the Vermont Oxford Network experience. Pediatrics. 1999;104(3 Pt 1):428-34.
22. Campbell ME, Byrne PJ. Cardiopulmonary resuscitation and epinephrine infusion in extremely low birth weight infants in the neonatal intensive care unit. J Perinatol. 2004;24(11):691-5.
23. Frontanes A, García-Fragoso L, García I, Rivera J, Valcárcel M. Outcome of very-low-birth-weight infants who received epinephrine in the delivery room. Resuscitation. 2011;82(4): 427-30.
24. Anju TR, Anitha M, Chinthu R, Paulose CS. Cerebellar GABA(A) receptor alterations in hypoxic neonatal rats: Role of glucose, oxygen and epinephrine supplementation. Neurochem Int. 2012;61(3):302-9.
25. Raveendran AT, Skaria PC. Learning and cognitive deficits in hypoxic neonatal rats intensified by BAX mediated apoptosis: protective role of glucose, oxygen, and epinephrine. Int J Neurosci. 2013;123(2):80-8.
26. Anju TR, Ajayan MS, Paulose CS. Disruption of cerebellar cholinergic system in hypoxic neonatal rats and its regulation with glucose, oxygen and epinephrine resuscitations. Neuroscience. 2013;236:253-61.