Endotracheal Delivery of Medications During Neonatal Resuscitation

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Most newborn infants do not require resuscitation in the delivery room, and the few who do need assistance typically respond to effective positive-pressure ventilation \cite{1,2}. Although the need for cardiopulmonary resuscitation and medications in the delivery room is rare, the consequences of such a hypoperfused state are often profound. It is vital that recommendations for resuscitation medications, dosages, and routes of delivery are based on the best possible science. Epinephrine has long been the preferred adrenergic agonist for the treatment of neonatal cardiac arrest that is resistant to effective ventilation. Effective administration of epinephrine leads to increased coronary perfusion pressure, increasing myocardial blood flow, which is crucial to re-establishing return of spontaneous circulation. Consequently, during cardiac arrest, epinephrine should be given by the most accessible route that delivers the drug effectively to the heart.

Endotracheal tube delivery of epinephrine is used frequently in the delivery room because intravenous access is not immediately available for most newborns \cite{3}. Many pediatric providers are more experienced and confident in placement of an endotracheal tube than in rapid placement of an umbilical venous catheter for medication delivery. Several factors could contribute, however, to a slower onset of action with endotracheal epinephrine in depressed newborns, including (1) decreased blood flow (which may be insufficient to transport drugs from the alveoli...
to the central circulation); (2) pulmonary vasoconstriction from acidosis during cardiac arrest or the epinephrine itself, which could impede drug absorption; (3) persistent alveolar fluid that dilutes the epinephrine; and (4) potential right-to-left intracardiac shunts that could bypass the pulmonary circulation altogether [4]. Despite such concerns, previous guidelines from the International Liaison Committee on Resuscitation stated that the recommended intravenous or endotracheal dose of epinephrine was 0.1 to 0.3 mL/kg of a 1:10,000 solution (0.01–0.03 mg/kg), repeated every 3 to 5 minutes as indicated [5]. Endotracheal medication delivery has been recommended for newborns in one additional clinical scenario. If a mother receives a narcotic drug during labor, and the infant’s vital signs have been established, but respiratory drive is considered inadequate despite positive-pressure ventilation, naloxone may be indicated. The previous International Liaison Committee on Resuscitation guidelines suggested that naloxone could be given intravenously, endotracheally, or intramuscularly at the dose of 0.1 mg/kg of a 0.4 or 1 mg/mL solution [5]. Although these recommendations for endotracheal medication delivery have been in practice for years, what scientific evidence exists to support them?

Questions

• Is there evidence that 0.01 to 0.03 mg/kg of endotracheal epinephrine followed by 0.5 to 1 mL normal saline flush is effective in establishing return of spontaneous circulation in newborns with a heart rate less than 60 beats/min despite 30 seconds of assisted ventilation and another 30 seconds of coordinated chest compressions and ventilation?

• Is there evidence that 0.1 mg/kg of endotracheal naloxone followed by 0.5 to 1 mL normal saline flush is effective in reversal of newborn respiratory depression if there is severe respiratory depression after positive-pressure ventilation has restored a normal heart rate and color and there is a history of maternal narcotic administration within the past 4 hours?

Evidence review

To address these questions, the available scientific literature was critically reviewed using Medline (PubMed), Embase, and Cochrane Systematic Reviews. Review studies were hand-searched for additional references. Search criteria included neonatal human and animal studies. Search terms used were newborn (neonatal) resuscitation, epinephrine, adrenaline, naloxone, and endotracheal. Non-English reports and single case reports were excluded. The search subsequently was limited to articles with some content regarding one of the two above-stated questions. A total of 65 articles were evaluated, but only 31 met final criteria for inclusion in this review.
Absorption of endotracheal epinephrine in animal models and patients with intact circulation

Several investigators have shown that epinephrine can be delivered via an endotracheal tube, and that some absorption from the pulmonary circulation occurs as shown by increases in epinephrine levels and heart rate and blood pressure above baseline in nonarrest models that received at least 10 times the currently recommended neonatal dose [6–8]. Manisterski et al [9] compared five different doses of endotracheal epinephrine ranging from 0.02 to 0.3 mg/kg in healthy anesthetized dogs. Only the 0.3 mg/kg dose (10–30 times higher than the currently recommended dose range) caused an increase in blood pressure that was sustained for at least 10 minutes. Paret et al [10] also noted no change in heart rate or blood pressure using 0.02 mg/kg of endotracheal epinephrine with a variety of diluents in healthy adult dogs.

Anesthetized adults with adequate blood pressure (and presumably adequate pulmonary perfusion) who prospectively received small doses of intravenous epinephrine also showed increases in heart rate and blood pressure, but had less predictable responses even though 5 to 10 times higher doses were given via endotracheal tube. McCrirrick and Kestin [11] reported no response to endotracheal epinephrine, and Raymondos et al [12] showed an increase in blood pressure. In a randomized crossover trial of 14 infants who were intubated for open heart surgery, endotracheal administration of 0.003 mg/kg increased mean arterial blood pressure, but the increase occurred later and was less consistent than after 0.0003 mg/kg of epinephrine given intravenously (very small doses) [13]. These studies support the concept that epinephrine can be given via endotracheal tube and is absorbed to some degree when there is adequate pulmonary perfusion. Even with intact circulation, endotracheal delivery requires much higher dosing than intravenous delivery, however, to achieve a response in blood pressure. In addition, the results may not translate to the neonatal cardiopulmonary arrest situation in which pulmonary blood flow is profoundly reduced or in which significant amounts of alveolar fluid persist.

Efficacy of endotracheal epinephrine during cardiac arrest from arrhythmia

In 1967, Redding et al [14] suggested that equivalent doses of endotracheal epinephrine would be as effective as intravenous epinephrine in achieving return of spontaneous circulation after adult cardiac arrest (which is most commonly due to ventricular fibrillation). Most subsequent studies have shown, however, that during cardiac arrest endotracheal epinephrine is absorbed slowly and erratically [15–18]. Given the findings in nonarrest models, most investigators using arrest models also report that much higher doses of endotracheal epinephrine are required to achieve increased plasma epinephrine concentrations and return of spontaneous circulation compared with intravenous epinephrine [16,18,19]. Crespo et al [18] showed that 0.01 mg/kg of endotracheal epinephrine (the low
end of the recommended neonatal epinephrine dose) was no better than placebo in re-establishing perfusion, using an adult model of ventricular fibrillation–induced cardiac arrest. Using an adult model of electromechanical dissociation, Ralston et al [16] showed that even 0.03 mg/kg of endotracheal epinephrine (the high end of the neonatal recommended dose) was insufficient to achieve return of spontaneous circulation. Only by an increase to 30 times the recommended dose of endotracheal epinephrine was return of spontaneous circulation achieved at rates similar to intravenous epinephrine.

Newborn piglets subjected to ventricular fibrillation (rarely a cause of newborn cardiac arrest) and treated with 0.01 mg/kg of endotracheal epinephrine (currently recommended dose) did not increase plasma concentrations of epinephrine or mean arterial blood pressure and did not achieve return of spontaneous circulation any better than placebo [20]. Hornchen et al [19] achieved rates of return of spontaneous circulation comparable to intravenous epinephrine with 10 times the currently recommended endotracheal epinephrine dose. Of concern, however, animals that received endotracheal epinephrine experienced significantly higher blood pressure and heart rate for a longer time than the intravenous group after return of spontaneous circulation. It has been postulated that during cardiopulmonary resuscitation (CPR) with endotracheal epinephrine administration, a pulmonary epinephrine depot may develop as a result of significantly decreased pulmonary perfusion. When spontaneous circulation is restored, there is potential for prolonged absorption of the epinephrine from the lungs into the pulmonary circulation with resultant prolonged, potentially dangerous side effects [16,19,21,22]. This situation could lead to marked increases in myocardial oxygen demand (at a time when recovery from the previous oxygen deficit is crucial) and could increase the risk for intraventricular hemorrhage in preterm neonates [23]. Lucas et al [24] examined the effects of hypoxia-induced low pulmonary blood flow on epinephrine absorption in newborn lambs and did not detect decreased pulmonary absorption of drug with hypoxia-induced blood flow reductions, but the animals were not in cardiac arrest. Studies of endotracheal epinephrine in adult humans with cardiac arrest are limited to a few small retrospective reviews that showed little or no benefit [25–27].

**Efficacy of endotracheal epinephrine during asphyxia-induced cardiac arrest**

In animal studies employing asphyxia as the cause for arrest (the most frequent cause of neonatal cardiopulmonary arrest), the rates of return of spontaneous circulation and elevation of mean arterial pressure are significantly lower with endotracheal epinephrine compared with intravenous epinephrine [14,28]. Jasani et al [29] could resuscitate successfully only 31% of asphyxiated, asystolic pigs with 0.05 mg/kg of endotracheal epinephrine.

Data supporting use of endotracheal epinephrine in human newborns requiring resuscitation are sparse and include three small, nonrandomized reports. The
first is a small cohort study examining pharmacokinetic degradation patterns after administration of 0.25 mg/kg of endotracheal epinephrine (25 times the recommended dose) in nine infants [30] who reportedly received resuscitation in the delivery room. Epinephrine levels were significantly elevated after endotracheal administration compared with infants who did not require epinephrine. In this cohort, epinephrine was used in only 29% of preterm infants requiring cardiopulmonary resuscitation with a reportedly low immediate mortality; this raises the possibility that the described population of infants may not have truly required the epinephrine. The study is one of absorption rather than efficacy.

The second study is a case series describing administration of 0.015 to 0.04 mg/kg of endotracheal epinephrine (slightly higher than recommended dose) in 10 infants [31]. All infants were bradycardic despite initial ventilation and CPR, but none were asystolic. In contrast to most experimental studies, in which endotracheal absorption was slow and erratic, the heart rate responded within 5 to 10 seconds of endotracheal epinephrine administration, raising the question of whether these infants truly required and responded to endotracheal epinephrine or merely needed continued ventilation. Three of the infants died (all were premature, and all died with intraventricular hemorrhage). Jankov et al [32] performed a retrospective analysis of all infants with birth weight 750 g or less over a 7-year period. Sixteen infants received CPR in the delivery room, of which 12 received endotracheal epinephrine. Overall, 9 of 16 survived, and 8 were free of severe neurologic disability at 2 years of age. Although this study seems encouraging, it is not possible to separate out the epinephrine data further, and the timing of the first dose of epinephrine varied from 1 to 15 minutes. This variability in timing raises the possibility of administration of endotracheal epinephrine before establishment of adequate airway and breathing. Four patients were excluded for receiving chest compressions before airway control and one for receiving epinephrine before chest compressions with a heart rate of greater than 100 beats/min. In addition, the median dose of endotracheal epinephrine used was 0.1 mg, which would be at least 10 times the currently recommended endotracheal dose for infants weighing 750 g or less.

There are similar difficulties when assessing the data from two nonrandomized case series of infants who required epinephrine during resuscitation [3,33]. Sims et al [33] reviewed 105 cases in which drugs were administered to neonates during resuscitation, but only 21 were in the delivery room. In total, only 14% of infants who required medication during resuscitation survived without significant handicap, but insufficient data were provided about use of endotracheal medication delivery. O’Donnell et al [3] described 78 infants who received epinephrine in the delivery room, of which a third survived without significant handicap. Epinephrine was delivered solely via the endotracheal tube in 82% and in combination with subsequent intravenous doses for an additional 12% of cases. Overall epinephrine use was more frequent (0.2%), however, than others have reported [1]. Local guidelines permitted the use of compressions or adrenaline before establishing airway and breathing, which makes efficacy difficult to interpret, especially because seven infants who received epinephrine had a
diagnosis of transient tachypnea of the newborn. These two studies offer evidence of potential harm in delaying adequate airway control and ventilation in an effort to give epinephrine. In 2003, Ziino et al. [34] attempted a meta-analysis of randomized controlled trials involving epinephrine use for resuscitation of neonates for the Cochrane Database and were unable to identify a single prospective clinical trial.

Efficacy of endotracheal naloxone reversal of opiate-induced respiratory depression

There are no human neonatal reports or neonatal model studies of endotracheal naloxone use. There is one small animal case series of four preventilated adult rabbits in which 0.1 mg/kg of naloxone given endotracheally successfully reversed morphine-induced respiratory depression as measured by mean minute ventilation [35].

Interpretation of the data

• There are no randomized trials using endotracheal epinephrine in neonates or appropriate neonatal models.
• The one neonatal cohort trial and one case series that showed absorption and benefit of endotracheal epinephrine used significantly higher doses than currently recommended.
• Almost every animal trial that showed any kind of positive effect of endotracheal epinephrine used 5 to 30 times the currently recommended dose.
• The one neonatal model study that used the currently recommended dose showed no benefit.
• The endotracheal route for naloxone has been evaluated in adults; however, there is no evidence for use of this route of administration in neonates.
• Two neonatal outcome studies raise concern that use of the endotracheal route inadvertently may facilitate use of epinephrine before adequate airway control and ventilation has been provided.

Potential translation of data into guidelines for clinical practice

• If the endotracheal route is to be used for administration of epinephrine, the limited available evidence suggests that a higher dose than the currently recommended 0.01 to 0.03 mg/kg dose would be needed.
• Given the paucity of high-quality clinical data regarding endotracheal epinephrine, the intravenous route should be used as soon as venous access is established.
• Given the complete lack of clinical data in newborns, endotracheal administration of naloxone is not recommended.
Knowledge Gaps

- Randomized trials are urgently needed in appropriate neonatal clinical settings or neonatal models of cardiopulmonary arrest secondary to asphyxia to determine the efficacy, dosing, and safety of endotracheal epinephrine delivery.
- Does early tracheal epinephrine affect ventilation?
- Does use of endotracheal epinephrine delay establishment of intravenous access?
- What diluent and how much volume of diluent are most efficacious for endotracheal epinephrine delivery?
- Is there a lower gestational age limit for which epinephrine is not beneficial by any route of delivery?

References


[34] Ziino AJ, Davies W, Davis PG. Epinephrine for the resuscitation of apparently stillborn or extremely bradycardic newborn infants. Cochrane Database Syst Rev 2003;CD003849.