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Bioavailability of Endotracheal Epinephrine in an Ovine Model of Neonatal Resuscitation

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Abstract

Background: Distressed infants in the delivery room and those that have completed postnatal transition are both resuscitated according to established neonatal resuscitation guidelines, often with endotracheal (ET) epinephrine at the same dose. We hypothesized that ET epinephrine would have higher bioavailability in a post-transitional compared to transitioning newborn model due to absence of fetal lung liquid and intra-cardiac shunts.

Methods: 15 term fetal (transitioning newborn) and 6 postnatal lambs were asphyxiated by umbilical cord and ET tube occlusion respectively. Lambs were resuscitated after 5 minutes of asystole. ET epinephrine (0.1mg/kg) was administered after 1 min of positive pressure ventilation (PPV) and chest compressions, and repeated 3 min later, followed by intravenous (IV) epinephrine (0.03mg/kg) every 3 min until return of spontaneous circulation (ROSC). Serial plasma epinephrine concentrations were measured.

Results: Peak plasma epinephrine concentrations were lower in transitioning newborns as compared to postnatal lambs: after a single ET dose (145.36±135.5ng/ml vs 553.54±215ng/ml, $p<0.01$) and after two ET doses (443±192.49ng/ml vs 1406±420.8ng/ml, $p<0.01$). The rates of ROSC with a single ET dose were similar in both groups (40% vs 50% in newborn and postnatal respectively, $p>0.99$). There was a higher incidence of post-ROSC tachycardia and increased carotid blood flow in the postnatal group.

Conclusions: In the postnatal period, ET epinephrine at currently recommended doses resulted in higher peak epinephrine concentrations, post-ROSC tachycardia and cerebral reperfusion

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without significant differences in incidence of ROSC. Further studies evaluating the optimal dose of ET epinephrine during the postnatal period are warranted.

Keywords

Neonatal resuscitation; endotracheal epinephrine; epinephrine concentration; lung liquid

1. Introduction:

Resuscitation of newly born infants in the delivery room and postnatal period is guided by the Neonatal Resuscitation Program (NRP)(1) in the United States. The recommended route for epinephrine is intravenous (IV) at a dose of 0.01-0.03 mg/kg. However, administration of a higher dose (0.05 to 0.1 mg/kg) through the endotracheal tube (ETT) may be considered while IV access is established (2). Due to infrequent use, the pharmacokinetics, safety and efficacy of endotracheal (ET) epinephrine has not been thoroughly evaluated in clinical studies (3).

Compared to the IV route, ET epinephrine has demonstrated less efficacy as indicated by low rates of return of spontaneous circulation (ROSC) and need for higher doses administered to potentially compensate for the decreased absorption and dilution by lung liquid present at birth (4). Additionally, lower concentrations of epinephrine are detected in plasma when it is administered endotracheally (5). A retrospective cohort study comparing the efficacy of a higher ET epinephrine dose (0.05mg/kg) to a lower dose (0.03 mg/kg) during neonatal CPR noted that a greater total epinephrine dose was needed before ROSC when the initial dose was administered via ET (6). In the NRP guidelines, the dose of ET epinephrine has increased from 0.01-0.03 mg/kg in 1999 to the currently recommended dose of 0.05-0.1 mg/kg in 2010 (7), based on limited data suggesting that higher doses are required for efficacy when used via ET in the delivery room setting (8, 9). Similarly, the Pediatric Advanced Life Support-PALS (10) (0.1 mg/kg) and Advanced Cardiovascular Life Support-ACLS (2-2.5mg) (11) guidelines also recommend higher doses of epinephrine via ETT. The corresponding IV doses are 0.01 mg/kg in children (PALS) and 1 mg in adults (ACLS).

Studies have shown that higher doses of epinephrine lead to several adverse effects. Besides an association with higher mortality in an animal model (12), high dose epinephrine has been shown to cause severe rebound tachycardia, hypertension and ventricular arrhythmias following ROSC (13). The presence of fetal lung fluid and high pulmonary vascular resistance with low pulmonary blood flow may impair absorption of ET epinephrine at birth (14). During postnatal resuscitation, however, epinephrine is delivered to air filled expanded lungs with low pulmonary vascular resistance and high pulmonary blood flow. Currently, the same dose of ET epinephrine is recommended at birth and during the postnatal period in spite of these physiological differences. We hypothesized that plasma concentrations following ET epinephrine would be higher in postnatal lambs that have completed transition compared to newborn lambs. We further hypothesized that higher plasma epinephrine concentrations would be associated with an increased incidence of ROSC but also hemodynamic adverse effects in postnatal lambs.

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2. Methods:

2.1 Surgery and instrumentation:

The study was approved by the Institutional Animal Care committee (IACUC) at University at Buffalo and methods were consistent with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). Time-dated ewes at 142 to 145 d gestation (full term 147 d) from May Family Enterprises (Buffalo Mills, PA) were fasted overnight, then induced for anesthesia with intravenous diazepam and ketamine. The ewes were intubated with a 10.0-mm cuffed ETT and ventilated with 2%-3% isoflurane with a rate of 16 breaths per minute. The ewes were continuously monitored with a pulse oximeter and an end-tidal CO_2 monitor. Fifteen fetal lambs were partially exteriorized, intubated and excess lung fluid in the ETT drained by gravity by tilting the head to the side to simulate decrease in lung liquid with labor. Thereafter, the ETT was occluded to prevent air exchange with gasping. Fetal lambs were instrumented as described previously (4, 15) with catheters placed in the right carotid artery and jugular vein for blood pressure measurements and blood draws. A 2-mm flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the left carotid artery to measure carotid blood flow. Electrocardiogram (EKG) leads were attached to the right axilla, left axilla, and right inguinal area (3-lead EKG). The ECG100C (Biopac Systems, Inc.) was used with Acknowledge Software to record EKG. Preductal pulse oximetry was measured using a Masimo radical pulse oximeter sensor (Masimo, Irvine, CA). Asphyxia was induced by umbilical cord occlusion using a vascular occluder. In the postnatal group, six (1-3 d old) lambs were similarly instrumented under isofluorane anesthesia, after premedicating with diazepam and ketamine, and asystole induced by ETT occlusion.

In this manuscript, we refer to transitioning lambs soon after delivery as “newborn” lambs and 1-3 day old lambs as “postnatal” lambs. We also compared these two groups to historical newborn lambs that received IV epinephrine at 0.03mg/kg dose (4).

2.2 Resuscitation:

Resuscitation was initiated after 5 min of asystole. Asystole was defined by a flat arterial pressure tracing and confirmed by the absence of an audible heart rate (HR) on auscultation. Prior studies in our lab have shown that lambs with a shorter period of asystole are successfully resuscitated without need for epinephrine administration; hence we chose a 5 min asystole period. Ventilation was begun using a T-piece resuscitator with 21% O_2 at a rate of 40 breaths/min and initial pressures of 35/5 cm H2O. Peak inspiratory pressure (PIP) was adjusted as needed to obtain adequate chest rise. Chest compressions were initiated after 30 sec of effective ventilation and inspired O_2 was increased to 100%. The initial dose of epinephrine at 0.1mg/kg (volume- 0.1 mg/ml) was administered at 1 min after 30 sec of chest compressions through the ETT and a second dose was given by ETT 3 min after the first dose. A third dose of epinephrine, if needed, was administered IV (0.03mg/kg) 3 min after the second ET dose. Subsequent epinephrine doses were given IV every 3 minutes thereafter until ROSC or 20 min from the onset of resuscitation. ROSC was defined as a sustained HR of >100 beats/min. Blood gases were drawn at asystole (prior to initiation of resuscitation) and then every minute during resuscitation until ROSC followed by q5 min

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gases till the end of the observation period. Arterial blood gases were analyzed using a radiometer blood gas analyzer (ABL 800 FLEX, Denmark). Lambs were monitored for a maximum of 30 min from birth and then sacrificed using pentobarbital per approved lab protocols. Physiological parameters including HR, systemic blood pressure (BP) and vascular flows were continuously recorded using AcqKnowledge Acquisition & Analysis Software (BIOPAC systems, Goleta, CA).

2.3: Epinephrine concentrations:

Plasma samples to measure free epinephrine concentrations were drawn prior to injection of the medication and every minute thereafter and analyzed by ELISA (Eagle Biosciences, cat# EA604/96). Adrenaline is extracted using a cis-diol-specific affinity gel, acylated to N-acyladrenaline and then converted to N-acylmetanephrine in this assay.

2.4: Statistical analysis and power calculation:

We based our power calculation on a previous study of plasma epinephrine levels following a single dose of ET epinephrine in newborn lambs (4). We speculated that a difference of 100 ng/ml in peak epinephrine levels would be considered clinically significant. Our sample size of 6 experimental and 15 control lambs provided a probability (power) of 0.9 with an alpha of 0.05.

Continuous variables were expressed as mean and standard deviation and analyzed by ANOVA between groups with Fisher's post hoc test. Categorical variables were analyzed using chi square test with Fisher's exact test if appropriate. GraphPad Prism (San Diego, CA) was used for statistical analysis. Statistical significance was defined as $p<0.05$.

3. Results:

Baseline characteristics for all lambs are shown in Table 1. The newborn and postnatal groups were similar in demographics such as birth weight, sex distribution and multiplicity. Physiological parameters such as blood pressure, heart rate and carotid flow were also comparable prior to the start of the experimental protocol. Transitioning newborn lambs had a significant amount of excess lung liquid drained by gravity prior to the start of resuscitation.

3.1 Return of spontaneous circulation:

40% of newborn and 50% of postnatal lambs achieved ROSC with the first dose of ET epinephrine (Fig 1). This number is lower than the 77% ROSC seen with initial IV dose of 0.03 mg/kg in historical newborn controls with the same model in our laboratory (4) ($p <0.01$ vs single dose ET newborn by fishers exact test). 66% of newborn and 83% of postnatal lambs achieved ROSC after the second ET epinephrine dose. The third dose of epinephrine administered IV at 0.03 mg/kg resulted in ROSC in all lambs in both groups. Overall ROSC percentages with subsequent ET and IV epinephrine were similar in both groups (Table 2). Time to achieve ROSC (after onset of positive pressure ventilation) was similar between the two groups (5.04±2.15 vs 5.24±2.50 min in newborn vs postnatal)

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3.2 Plasma Epinephrine concentrations:

Peak epinephrine concentrations after a single ET dose (145.36±135.5 ng/ml vs 553.54±215 ng/ml, $p<0.01$) as well as a second ET dose (443±192.49 ng/ml vs 1406±420.8 ng/ml, $p<0.01$) were significantly lower in newborn as compared to postnatal lambs (Fig 2a, 2b). There was no significant difference noted in the pattern of rise in epinephrine levels with time following ET dosing in the two groups (p=NS by repeated measures ANOVA) (Fig 3). Compared to historical newborn controls that received only IV Epinephrine, the peak in plasma epinephrine levels after ET dose appears delayed (Fig 3).

3.3 Relation to ROSC:

We evaluated the patterns of plasma epinephrine rise in relation to ROSC in lambs that received only a single dose of ET epinephrine (n=6 newborn and n=3 postnatal). Plasma epinephrine concentrations in newborn lambs receiving ET epinephrine peaked between 4-10 minutes after drug administration and after ROSC. In the postnatal lambs, epinephrine concentrations peaked between 2-3 minutes after administration and immediately after ROSC. Historical newborn lambs (n=8) that received an initial IV dose of epinephrine (0.03 mg/kg) reached a peak epinephrine concentration within a minute of administration of the medication and just prior to ROSC suggesting rapid bioavailability (Fig 4).

3.4 Hemodynamic parameters:

We evaluated hemodynamic parameters, specifically carotid blood flow (CaBF), HR and BP in the two study groups of lambs receiving ET epinephrine only, at various times points during the delivery, resuscitation and immediate post resuscitation period (Fig 5). CaBF was similar in both groups until ROSC. However, significantly higher CaBF was observed in the postnatal group after ROSC (Fig 5a). Additionally, significantly higher heart rates including severe tachycardia (> 300 bpm) were seen in the postnatal group after ROSC (Fig 5b). There were no statistically significant differences noted in the systolic or diastolic blood pressures during the study period between the two groups (Fig 5c and d).

4. Discussion:

Ethical concerns and the infrequent use of epinephrine in newborns creates a challenge for designing randomized and masked clinical trials on this subject. Therefore, currently, observational and animal studies provide the highest level of evidence guiding clinical practice. To our knowledge, this is the first study comparing pharmacokinetics following ET epinephrine in a newborn and postnatal model of cardiac arrest induced by asphyxiation. Our data suggest higher plasma epinephrine concentrations and adverse hemodynamic effects (severe tachycardia and increased CaBF) in postnatal lambs that received 0.1mg/kg of ET epinephrine. Contrary to our hypothesis, in spite of the higher plasma concentrations, there was no difference in the incidence or timing of ROSC between the two groups. Therefore, we suspect that factors other than plasma epinephrine concentrations may influence ROSC. These could include oxygenation, ventilation and hemodynamic parameters, including blood pressures generated during resuscitation and other factors that influence coronary perfusion and myocardial oxygen delivery. The role of the mitochondria and tissue adenosine triphosphate (ATP) in arrest and resuscitation has also been recognized

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and investigated. Impairment of mitochondrial respiration and partial depletion of ATP and phosphocreatine (PCr) has been noted in rodents following a prolonged cardiac arrest(16). Restoration of depleted myocardial ATP and energy stores could influence outcome of resuscitation(17).

There is limited information on whether infants who have completed transition from fetal to neonatal circulation should be resuscitated using the same guidelines and principles that apply to newborns in the delivery room. Newborn infants have decreased pulmonary blood flow with a patent ductus arteriosus (shunting right to left), high pulmonary pressures and fluid-filled lungs (18). These physiological differences may interfere with drug absorption, thereby decreasing the bioavailability of medications administered via the endotracheal route. A recent survey has reported that infants at the same age and with a similar etiology of cardiac arrest are resuscitated using neonatal guidelines when cared for in the NICU, whereas infants in the pediatric and cardiac intensive care units are resuscitated using pediatric guidelines (19). Since the current PALS guidelines also recommend a dose of 0.1 mg/kg (max 2.5 mg) via the ET route (20), our observations may be applicable to pediatric patients that receive ET epinephrine.

Our study groups showed differences in peak concentrations (Fig 1, 2, 3), suggesting that the physiological differences of transitional circulation likely affect absorption of this medication. We speculate that newborn lungs, filled with liquid and poorly perfused, act as a depot or reservoir for epinephrine. The rapid improvement in pulmonary blood flow that occurs with ROSC likely results in improved absorption of epinephrine, leading to delayed peak concentrations. Conversely, the lack of lung liquid and resolution of active fetal shunts such as the ductus arteriosus in postnatal lambs could explain earlier peak plasma epinephrine concentrations that were noted around ROSC.

We have explored a relationship between plasma epinephrine levels and ROSC in our study that is not well described in the literature. With very frequent sampling of plasma epinephrine concentrations and real-time data collection allowing accurate determination of time of ROSC, we were able to plot plasma epinephrine levels before and after ROSC. A clear difference is noted with the postnatal group showing peak levels coinciding with ROSC, while the newborn group at birth shows a delayed surge (beyond 4min after ROSC). However, we acknowledge that our study does not prove a direct relationship between epinephrine levels and ROSC, as incidence and timing of ROSC were similar between the study groups. Additionally, similar to prior studies, we are unable to identify any threshold epinephrine level that would correlate with increased probability of ROSC.

Halling et al reported that one dose of ET epinephrine (0.03 to 0.05 mg/kg) was associated with ROSC in 6/30 (20%) infants in the delivery room. A canine study comparing different routes of epinephrine showed high ROSC rates with ET (90%) vs controls without vasopressors (20%) (21), however these subjects were older mongrel dogs exhibiting postnatal physiology. We have noted ROSC rates of 40% and 50% in our transitioning newborn and postnatal groups with a single dose ET epinephrine. These findings support the current NRP recommendation of administering one dose of ET epinephrine, while attempting IV access both in transitioning newborn as well as in postnatal resuscitation.

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Multiple ET doses administered to a fluid-filled lung could have a cumulative effect and potentiate toxicity. When evaluating plasma epinephrine concentrations in our study lambs that received an IV dose after 2 ET doses (n=5 in newborn and n=1 in postnatal), peak values of 1287±534 ng/ml in the newborn group were noted. The postnatal lamb, however, had a very high peak concentration at 3496 ng/ml. While it is difficult to compare these groups with only 1 postnatal lamb requiring IV epinephrine, the high concentration attained with multiple doses of epinephrine is concerning.

Health care providers need to be cognizant of the potential serious adverse hemodynamic effects from high dose epinephrine administration during resuscitation. Tachyarrythmias after ET epinephrine have been previously reported (4). Higher doses of epinephrine have been shown to be associated with severe rebound tachycardia, hypertension and ventricular arrhythmias following ROSC (13) with IV as well as endotracheal routes. Our results corroborate these findings, as we have shown severe tachycardia and higher CaBF in the postnatal lambs, which correspond to higher plasma epinephrine concentrations. Post asphyxial cerebral hyperemia can further potentiate neuronal injury after the initial hypoxic ischemic insult (22). The higher CaBF noted at 2 and 5 min post ROSC in the postnatal lambs is concerning and warrants cautious use of ET epinephrine, especially after the period of perinatal transition. Increased cerebral flow would be particularly concerning in premature infants who have impaired cerebral autoregulation and are at increased risk of intraventricular hemorrhage.

We did not observe any significant differences in blood pressure between our study groups after ET epinephrine though prior studies have raised concerns for potential hypotension due to beta adrenergic effects (23). One of the limitations of our study is that we used the higher end of the NRP recommended epinephrine dose range (0.1 mg/kg ET and 0.03 mg/kg IV) and were unable to evaluate lower doses (0.05 mg/kg ET and 0.01 mg/kg IV) in this study. Further studies should be designed to evaluate the possibility of reducing the dose of ET epinephrine to 0.05 mg/kg, especially in the postnatal period to reduce the risk of adverse hemodynamic events. Additionally, since our study lambs did not have parenchymal lung disease, we are unable to speculate on the absorption and effects of ET epinephrine in newborns with concurrent pathologies such as meconium aspiration or other parenchymal lung diseases.

5. Conclusions

The use of high dose ET epinephrine (0.1 mg/kg) in a post transition 1-3 d lamb model of asphyxial cardiac arrest resulted in higher peak plasma epinephrine concentrations, post-ROSC tachycardia and increased CaBF that could potentially exacerbate reperfusion neuronal injury without improved incidence of ROSC compared to newborn lambs. Epinephrine administration via endotracheal route at the higher range (0.1 mg/kg) of the currently recommended dose (0.05-0.1 mg/kg) should be used with caution in the postnatal period after resorption of lung liquid. Repeated doses of ET epinephrine can result in high peak plasma concentrations. Our findings reinforce the need for further clinical studies that can assist in optimization and tailoring of ET epinephrine use and dosing (24), depending on postnatal age as well as circumstances of neonatal arrest.

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Highlights

- Peak plasma epinephrine concentrations after endotracheal epinephrine are significantly lower in transitioning newborn lambs as compared to postnatal lambs.
- Postnatal lambs that received endotracheal epinephrine had a higher incidence of post resuscitation tachycardia and increased carotid blood flow when compared to transitioning newborn lambs.
- Epinephrine administration via endotracheal route at the higher range (0.1 mg/kg) of the currently recommended dose (0.05-0.1 mg/kg) should be used with caution in the postnatal period.
- There is a need for further studies to assist in optimization and tailoring of ETT epinephrine use and dosing, depending on postnatal age as well as circumstances of neonatal arrest.

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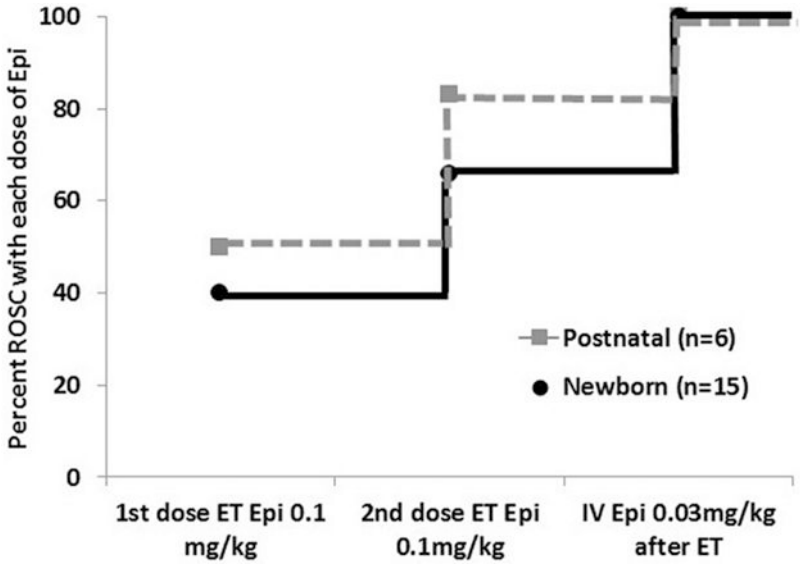

Figure 1:

Cumulative percentage of lambs attaining ROSC (return of spontaneous circulation) following each dose of epinephrine (epi). Lambs received initial ET epi (n=15 newborn, n= 6 postnatal), 2nd ET (n=9 newborn, n=3 postnatal) and a 3rd dose IV (n=5 newborn, n=1 postnatal) prior to ROSC.

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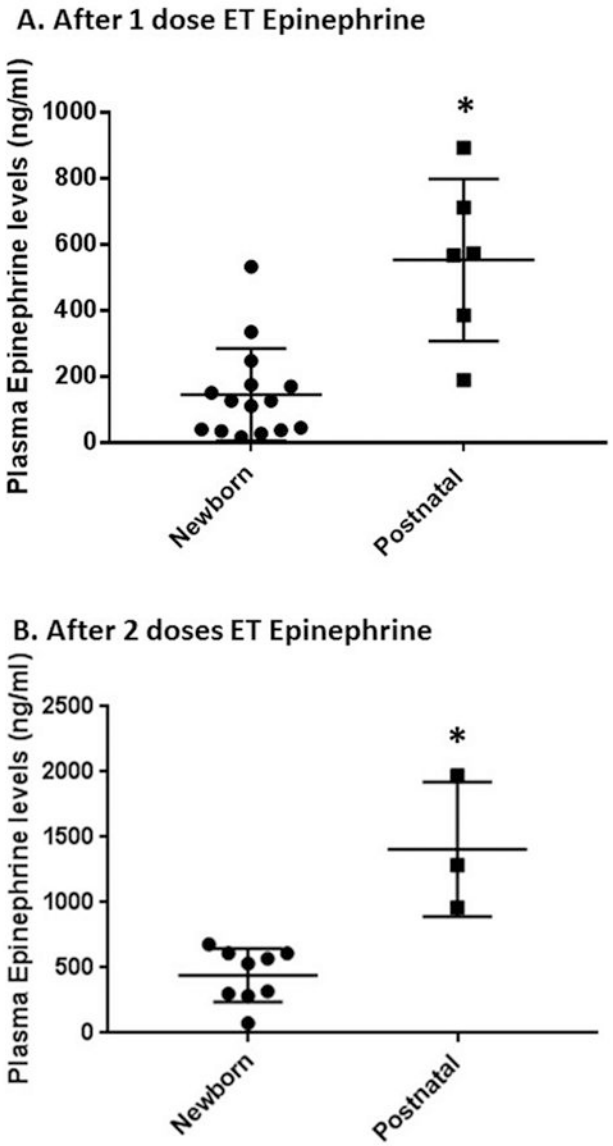

Figure 2: Highest plasma epinephrine levels in the study groups

A. after first dose ETT epinephrine and prior to administration of the second dose in some lambs (highest level achieved between minute 1-4 after onset of positive pressure ventilation - n=15 newborn, n= 6 postnatal)

B. after second dose ETT epinephrine and prior to IV epinephrine in some lambs (highest level achieved between minutes 4-7 after onset of positive pressure ventilation ● Newborn group (n=9) ■ Postnatal group (n=3). * $p<0.01$ vs newborn by Mann Whitney U test

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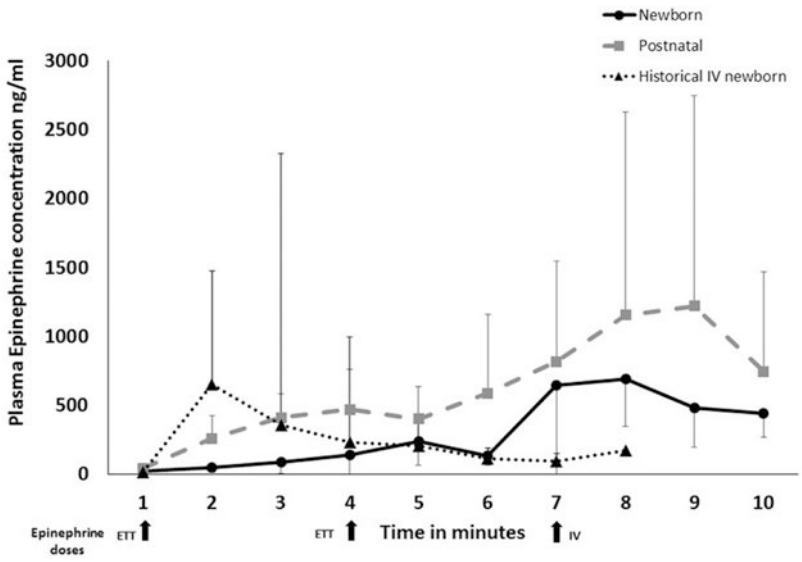

Figure 3:

Pattern of rise in plasma epinephrine concentrations over time following each dose of Epinephrine cumulatively in all lambs. ●Newborn group (n=15) ■ Postnatal group (n=6) ▲ Historical newborn lambs receiving only IV epinephrine (dose, 0.03 mg/kg - n=8)

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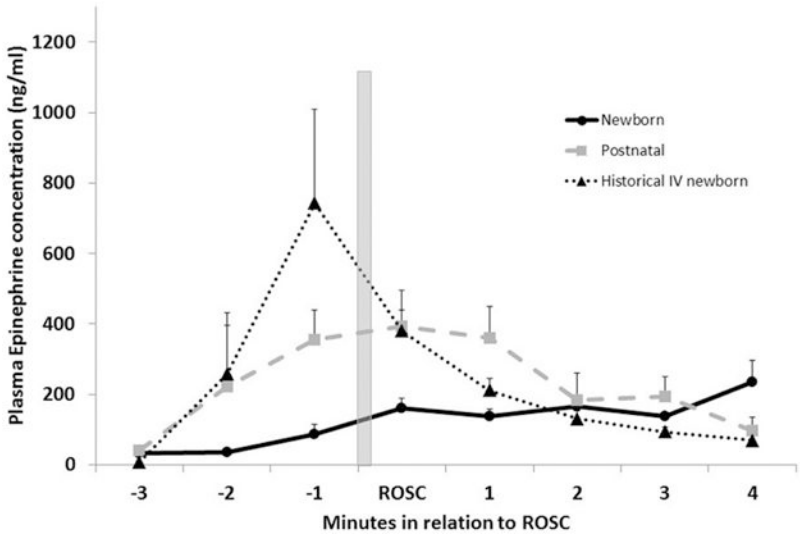

Figure 4:

Plasma epinephrine concentrations in relation to time of ROSC in lambs receiving only 1 dose epinephrine prior to achieving ROSC ● ET Newborn group (n=6) ■ ET Postnatal group (n=3)▲ Historical newborn lambs receiving only IV epinephrine (n=8). The vertical grey bar depicts time of ROSC.

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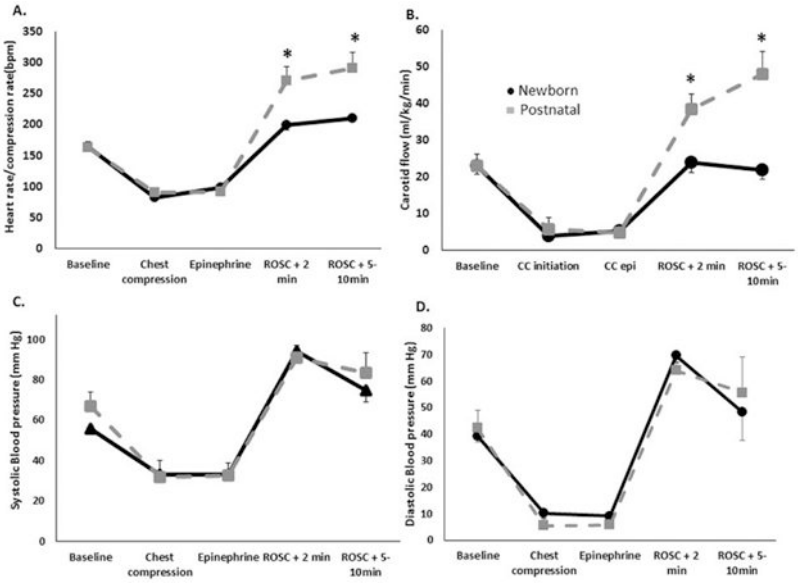

Figure 5:

Hemodynamic parameters in the study groups at various time points in lambs that received only ET epinephrine- baseline prior to resuscitation, during chest compressions, epinephrine administration and 2min and 5-10min after ROSC. A. Heart rate changes B. Carotid blood flow C. Systolic blood pressure and D. Diastolic blood pressure. ● Newborn group (n=10) ■ Postnatal group (n=5) * $p<0.01$ by Mann Whitney U test vs newborn at the same time point.

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Table 1:

Baseline characteristics

	Newborn (n=15)	Postnatal (n=6)
Weight (grams)	4060±810	3596±870
Male sex (%)	7/15 (47)	1/6(17)
Multiple gestation (%)	12/15 (80)	5/6 (83)
Lung liquid (ml)	65.2±28.6	0*
Physiological parameters		
Systolic Blood Pressure (mmHg)	55±11	67±15
Mean Blood Pressure (mmHg)	46±9	53±15
Diastolic Blood Pressure (mmHg)	39±8	42±15
Heart rate (bpm)	164±26	168±27
Carotid Flow (ml/kg/min)	23±9	25±8

* p <0.0001 by Mann Whitney test

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Table 2:

Percentage of Return of spontaneous circulation (ROSC) with each dose of epinephrine

ROSC with	Newborn (n=15)	Postnatal (n=6)	p value by fishers exact test
1st dose ETT epi 0.1mg/kg	6/15 (40%)	3/6 (50%)	>0.99
2nd dose ETT epi 0.1 mg/kg	4/9 (66%)	2/3 (83%)	>0.99
IV epi 0.03 mg/kg after ETT	5/5(100%)	1/1 (100%)	>0.99
Overall	15/15 (100%)	6/6 (100%)	>0.99