A Comparison of Intraosseous and Intravenous Adrenaline Administration During Resuscitation of Asphyxiated Newborn Lambs

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Abstract

Objective: Intraosseous access is recommended as a reasonable alternative for vascular access during newborn resuscitation if umbilical access is unavailable, but there are minimal reported data in newborns. We compared intraosseous with intravenous adrenaline administration, during resuscitation of severely asphyxiated lambs at birth.

Methods: Near-term lambs (139 days' gestation) were instrumented antenatally for measurement of carotid and pulmonary blood flow, and systemic blood pressure. Intrapartum asphyxia was induced by umbilical cord clamping, until asystole. Resuscitation commenced with positive pressure ventilation followed by chest compressions and lambs received either intraosseous or central intravenous adrenaline (10 micrograms/kg); adrenaline administration was repeated every 3 minutes until return of spontaneous circulation (ROSC). Lambs were maintained for 30 minutes after ROSC. Plasma adrenaline levels were measured before cord clamping, at end asphyxia, and at 3 and 15 minutes post-ROSC.

Results: ROSC was successful in 7/9 intraosseous adrenaline lambs and 10/12 intravenous adrenaline lambs. The time and number of adrenaline doses required to achieve ROSC were similar between groups, as were the achieved plasma adrenaline levels. Lambs in both groups displayed a similar marked overshoot in systemic blood pressure and carotid blood flow after ROSC. Blood gas parameters improved more quickly in the intraosseous lambs in the first 3 minutes, but were otherwise similar over the 30 minutes after ROSC.

Conclusions: Intraosseous adrenaline administration results in similar outcomes to intravenous adrenaline during resuscitation of asphyxiated newborn lambs. These findings support the inclusion of intraosseous access as a route for adrenaline administration in current guidelines.

Introduction

Worldwide, approximately 10 million infants per year require resuscitation at birth, which may include interventions such as stimulation, oxygen and positive pressure ventilation, or, in the most severe cases, chest compressions (CC) and drugs such as adrenaline.(1) The proportion of infants receiving adrenaline during neonatal resuscitation is difficult to define. Reports from a large tertiary centre in the United States suggest adrenaline use occurs at approximately 0.05% of births,(2, 3) whereas resuscitation guidelines quote figures of 1-3 per 1,000 term and late preterm births.(4) On a global scale this would equate to tens of thousands of infants annually, in settings where advanced neonatal resuscitation is available. Although representing a small proportion of births, these infants are at particularly high risk of major adverse outcomes such as neurodisability and death.(5)

While not clearly understood, the critical action of adrenaline during newborn resuscitation is thought to be the same as that derived from work in infant and adult animal models, specifically its effect on alpha-adrenergic receptors, resulting in systemic vasoconstriction.(6) Vasoconstriction, in conjunction with forward flow from CC,(7) results in increased aortic and coronary perfusion pressure, which correlates with myocardial perfusion and is a positive predictor of return of spontaneous circulation (ROSC).(8, 9)

Neonatal resuscitation guidelines include several potential routes for adrenaline administration, with intravenous (IV) administration via an umbilical venous catheter (UVC) preferred.(10, 11) Alternatives include administration via endotracheal tube, which may be placed early during resuscitation for airway management, or via intraosseous (IO) needle. IO access is an established alternative to IV access in resuscitation guidelines for adults and older children,(12, 13) but has featured less prominently in neonatal guidance, potentially reflecting a lack of evidence, availability, or familiarity in neonatal settings. A review of IO versus UVC adrenaline, conducted by the International Liaison Committee on Resuscitation (ILCOR) in

2020, identified no evidence comparing these two treatments in newborns.(10) The current ILCOR treatment recommendation is that IO access "is a reasonable alternative for vascular access during newborn resuscitation" at birth if umbilical access is unavailable, and that outside the delivery room, "either umbilical venous access or the IO route may be used".

Preclinical research can provide a vital understanding of the physiological effects of clinical treatments and, particularly in the context of a lack of clinical evidence, may influence treatment recommendations. We aimed to evaluate the efficacy of IO adrenaline administration during resuscitation, compared with IV administration, in a near-term lamb model of birth asphyxia.

Methods

Instrumentation and delivery

Pregnant Border-Leicester ewes (*Ovis Aries*) at (139 ± 2d) days gestation (mean±SD; term ~148 days) were anaesthetised with IV thiopentone sodium (20 mg/kg), followed by tracheal intubation and delivery of inhaled anaesthesia (isofluorane 1.5-2.5%).

The fetus was partially exteriorised (head and chest) from the uterus and flow probes were placed around the left main pulmonary artery, femoral artery and carotid artery (Transonic Systems, Ithaca, NY, USA). Catheters were inserted into a carotid artery and jugular vein (PD10; DTX Plus Transducer; Becton Dickinson, Singapore) as described previously.(14) Arterial pressures and blood flows were digitally recorded (1kHz, Powerlab; ADInstruments, Castle Hill, NSW, Australia). The fetal trachea was intubated with a 4.5mm cuffed endotracheal tube and lung liquid drained passively. A peripheral oxygen saturation (SpO_2) probe (Masimo, Radical 4, CA, USA) was placed around the right forelimb and a Near Infrared

Spectroscopy (NIRS) Optode (Casmed Foresight, CAS Medical Systems Inc, Branford, CT, USA) placed over the left frontal cortex to measure cerebral tissue oxygen saturation ($SctO_2$). For lambs allocated to IO treatment, an IO needle (Arrow EZ-IO 15mm 15ga IO needle, Teleflex Medical, Wayne PA, USA) was inserted in the distal right rear femur.

After delivery, asphyxia was induced by umbilical cord clamping, and continued until the mean blood pressure was reduced to ~0 mmHg and no discernible activity was visible on the blood pressure trace.(14) Resuscitation was initiated in air with a 30s sustained inflation to 30 cmH_2O, followed by positive pressure ventilation using a T-piece device (Neopuff; Fisher and Paykel Healthcare, Auckland, New Zealand) with peak inflation pressure 30 cmH_2O and end-expiratory pressure 5 cmH_2O, targeting 60 breaths per minute. One minute after ventilation onset, if heart rate remained <60 beats per minute, CC were initiated with a target of 90 CC and 30 ventilation breaths per minute, and fraction of inspired oxygen increased to 1.00 as per resuscitation guidelines.(11) Intravenous (jugular vein, n=12) or intraosseous (n=9) adrenaline (50 micrograms, equivalent to 10 micrograms/kg based on estimated weight 5 kg) was given 1 minute after CC were initiated, and every 3 min thereafter if ROSC had not been achieved, for a maximum of 4 doses. Treatment allocation to IV or IO adrenaline was determined by the investigators prior to surgery (not random) and was unblinded. In the IO group, after three IO adrenaline doses, a fourth and final 'rescue' IV dose was administered. Each adrenaline dose (by either route) was flushed with 5 ml of 0.9% saline.

After ROSC, lambs received pressure-limited volume guarantee ventilation at tidal volume 7ml/kg,(15) with heated humidified gas (Dräeger Babylog 8000+, Dräeger, Lübeck, Germany). Ventilation parameters were digitally recorded (Powerlab, as above). Lambs were sedated to maintain comfort (Alfaxan IV 5-15mg/kg/h in 5% dextrose). Blood gas samples (ABL30,

Radiometer, Copenhagen, Denmark) were collected every 3 minutes until 15 minutes, and every 5 minutes thereafter. Ventilation settings were adjusted to target SpO_2 90-95% and $PaCO_2$ 35-45 mmHg.

Plasma samples were collected from the carotid artery before cord clamping (fetal), at end of asphyxia, and 3 and 15 minutes after ROSC, and adrenaline concentrations were determined by enzyme immunoassay (Adrenaline 162 Research ELISA, LDN, Germany, catalogue #BA E-5100).(16) Lambs were humanely euthanised (sodium pentobarbitone >100mg/kg IV) at 30 minutes after ROSC.

Statistical analysis

Baseline fetal and physiological data were compared using a Student's t-test, or Mann-Whitney rank-sum test if data were not normalised (GraphPad Prism; GraphPad Software, CA, USA). A two-way repeated measures ANOVA with Holm-Sidak *post hoc* comparison was used to compare serial physiological data (SigmaPlot; Systat Software Inc., CA, USA). Statistical significance was accepted at $P < 0.05$. A minimum of 7 survivors per group was regarded as sufficient to determine differences in serial physiological variables, based on previous studies conducted by our group.

Results

Fetal Characteristics:

Fetal characteristics are outlined in Table 1. PaO_2 was significantly higher in IO animals compared to IV animals prior to initiation of studies. All other variables were similar in the two groups. The weights in each group were similar, but were slightly lower than the working weight used to calculate the adrenaline dose (5 kg). As a result, the administered mean

adrenaline dose was 12.2 micrograms/kg in the IV group, and 11.1 micrograms/kg in the IO group.

Table 1. Characteristics of all lambs, and those achieving ROSC (intravenous group 10/12 lambs, intraosseous group 7/9 lambs)

	All Lambs		Lambs Achieving ROSC	
	Intravenous	**Intraosseous**	**Intravenous**	**Intraosseous**
n	12	9	10	7
Birth Weight (kg)	4.0 ± 0.6	4.5 ± 0.8	4.1 ± 0.5	4.5 ± 0.8
Males	6/12	4/9	6/10	3/7
pH †	7.25 ± 0.07	7.26 ± 0.04	7.23 ± 0.06	7.26 ± 0.04
$PaCO_2$ (mmHg) †	56.4 ± 9.1	57.0 ± 5.9	57.2 ± 9.7	55.0 ± 3.6
PaO_2 (mmHg) †	19.6 ± 5.6	25.7 ± 6.6*	18.6 ± 5.5	27.3 ± 6.4*

Values are mean ± SD unless indicated

† At end of instrumentation and prior to asphyxia

* Indicates P <0.05

Resuscitation and Return of Circulation:

Achievement of ROSC occurred in 10/12 IV lambs and 7/9 IO lambs. The number of adrenaline doses received was similar in both groups: a single dose was required by 7/10 survivors in the IV group (range 1-3 doses), and 6/7 survivors in the IO group (range 1-2 doses). There was no difference in the time taken to achieve ROSC (Figure 1), with 8 lambs and 6 lambs achieving ROSC within 5 minutes in the IV and IO groups respectively.

Plasma Adrenaline Levels:

Plasma adrenaline was elevated at 3 minutes in comparison to the fetal and asphyxia levels, but was reduced again at 15 minutes. Plasma adrenaline concentrations were similar in the two groups at all measured timepoints (Figure 2).

Blood-gas, Oxygenation and Ventilation Parameters:

At 3 minutes, pH and PaO_2 were significantly higher, and $PaCO_2$ was significantly lower, in IO lambs compared to IV lambs (Figure 3). No differences were identified at other time points. Arterial lactate was significantly higher in IV lambs compared to IO lambs throughout the study (Group effect p=0.0032). Peripheral oxygen saturation and cerebral oxygenation, measured by pulse oximetry and NIRS respectively, were not different between groups at any time point, nor was FiO_2. Mean airway pressure was significantly higher in IV lambs than IO lambs throughout the study.

Physiological Parameters:

Blood pressure was not different between groups before or after ROSC (Figure 4). A pronounced overshoot in blood pressure beyond fetal values was observed in both groups (mean blood pressure increase: IO 24.2 ± 11.3 mmHg, IV 23.6 ± 21.0 mmHg), and the degree of overshoot was similar. Pulmonary and carotid blood flow were not different between groups. The overshoot in mean carotid blood flow was similar in the two groups (IO: 1134.5 ± 721.7 ml/min/g brain weight vs. IV: 716.5 ± 420.0 ml/min/g brain weight).

Discussion

Using asphyxiated near-term lambs, we have shown IO and IV adrenaline administration result in similar outcomes, in terms of achievement of ROSC and in the physiological responses seen shortly after resuscitation. The number of adrenaline doses required to achieve ROSC was

similar in both groups, as were the measured plasma adrenaline levels at all time points before and after ROSC. These data support the concept that medications administered via an IO device are rapidly distributed into the central venous circulation.

We found that blood gas parameters in the IO group improved more rapidly, with higher pH and PaO_2, and lower $PaCO_2$. These differences did not persist beyond 3 minutes after ROSC, so are unlikely to be clinically meaningful. Lactate was persistently higher in IV lambs than IO lambs throughout the study, although this was also true at end of asphyxia, despite other blood gas parameters in the two groups being similar. The reasons for this difference are unclear, and may represent random variation between lambs. Similarly, it was not apparent why the IO group required lower mean airway pressures, despite a consistent approach to ventilation in both groups.

Both groups had a marked increase in blood pressure and carotid blood flow in the minutes immediately after ROSC. This may be a reflection of the combined effect of systemic vasoconstriction due to adrenaline administration, and the physiological response of the fetus to asphyxia, which results in preferential maintenance of brain perfusion.(17, 18) Previous studies have shown a correlation between the overshoot in blood pressure and degree of cerebrovascular injury as assessed by protein leakage from subcortical white matter and grey matter.(17) The strategy of physiologically based cord clamping (PBCC), in which ventilation is commenced prior to cord clamping, reduces both blood pressure overshoot and cerebrovascular injury, in comparison with immediate cord clamping prior to resuscitation, as was used in this study. Resuscitation with the umbilical cord intact is currently restricted to clinical trials. Should this approach become more widely adopted into clinical practice, it is a

scenario in which IO access may prove very advantageous as the cord is not available for UVC insertion during PBCC.

Previous data on the use of IO access in the neonatal population are extremely limited. A recent systematic review identified one neonatal case series of 30 infants, and several case reports.(19) This review summarised the reported complications of IO placement, which include malposition, fracture, infection, compartment syndrome and limb ischaemia. Although these complications are important, if the alternative is failure to administer adrenaline, likely resulting in death, in most situations they would be deemed acceptable. UVC insertion has also been associated with complications, including infection, thrombi, hepatic injury, cardiac tamponade and death.(20, 21)

This is the first study, in either the clinical or preclinical setting, to compare the IO and IV routes for adrenaline administration during newborn resuscitation. The strengths of this study include the use of a well-established model that replicates the transitional physiology seen at birth in humans, including the liquid-filled newborn lung, changing pulmonary vascular resistance, and the presence of structural fetal shunts including a patent ductus arteriosus. Limitations in applicability to clinical care include that this study was conducted in lambs, which although of similar size to a term infant, have certain anatomical differences, and the lack of randomised treatment allocation. We used jugular rather than umbilical venous adrenaline administration, but both routes similarly provide central venous access. The controlled environment in which this study was conducted is a strength in terms of providing reliable physiological data, but cannot accurately replicate the stressful environment of a newborn resuscitation, where a variety of clinical, equipment, and human factors will influence outcome.(22)

Comparisons of IO and IV access via UVC have previously been described in simulation studies. These studies reported that IO access was achieved in a significantly shorter time than UVC placement, including when participants were practitioners specialising in newborn care, with greater experience of UVC placement than IO placement.(23-25) While it would be expected that these clinicians will preferentially choose a more familiar procedure (UVC) over an unfamiliar one (IO), and that complications of an unfamiliar procedure may be more frequent, both uptake in use and success rate without complication would be expected to increase with appropriate training. Including IO access more prominently in neonatal resuscitation training, alongside UVC insertion, may change decision making in clinical practice. Many infants who require resuscitation at birth are born outside of tertiary neonatal units and resuscitated by clinicians such as general paediatricians, midwives, anaesthetists, emergency clinicians, general practitioners or paramedics. These clinicians may have limited exposure to neonatal resuscitation, particularly UVC insertion. However, if regularly involved in resuscitation of adults or older children, they may be familiar with IO insertion as this approach is more prominent in resuscitation guidelines for these patient groups.(12, 13) It may be appropriate that treatment recommendations place more emphasis on prioritising either IO or IV access based on whichever route is likely to be achieved more rapidly, depending on the training and experience of the treating clinician. European guidelines, updated in 2021, feature the option of IO access more prominently than in past versions.(11)

While ideally clinical trials should be used to guide practice recommendations, there are situations where conducting such research is particularly difficult. The use of adrenaline during newborn resuscitation typically occurs unpredictably at a small minority of births, and must be administered as an emergency treatment, creating a particularly challenging environment for clinical research. In such situations, the use of alternative approaches to study design, such as

cluster trials, or the use of a waiver of informed consent, may be necessary to allow effective study recruitment. While clinical randomised trial data on the use of IO adrenaline is the optimal scenario, even additional observational clinical data would be informative, given the minimal existing evidence in the neonatal population.

Conclusions

In the absence of clinical evidence from human trials, appropriately designed preclinical research may influence treatment recommendations. In this study, conducted in asphyxiated near-term lambs, we found IO adrenaline administration resulted in similar outcomes to IV adrenaline, in terms of required dosage and plasma level, achievement of ROSC, and physiological parameters measured after ROSC. The results of this study provide reassurance that the physiological responses seen with IO adrenaline use during newborn resuscitation are very similar to those seen with IV adrenaline, currently regarded as the 'gold standard' route of administration, and support the inclusion of IO access as a route for adrenaline administration in current consensus guidelines.

CONTRIBUTOR STATEMENT

CTR, GMS, DAB, SB, CCR, MK, AWG, SBH and GRP made substantial contributions to study conception and design, or analysis and interpretation of the data. SK, KJC, KAR, VZ and AM contributed to data collection and analysis. CTR and GRP co-wrote the first draft of the manuscript. GRP created figures 1-4. All authors critically reviewed the manuscript for content, approved the final version, and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

We acknowledge the support of Teleflex Medical, who loaned the EZ-IO Power Driver, and donated the Arrow EZ-IO needles used in this study. Teleflex Medical had no input in study design, conduct, or analysis, or in manuscript preparation. The authors have no other conflicts to declare.

ETHICS APPROVAL

Experimental procedures were approved by Monash Medical Centre Animal Ethics Committee A, Monash University (MMCA/2018/10), were conducted in accordance with the National Health and Medical Research Council of Australia's guidelines, and are reported in accordance with the ARRIVE guidelines.(26)

DATA SHARING

Data are available to qualified researchers upon reasonable request to the authors.

LICENSING

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What is already known on this topic

- Adrenaline is required during resuscitation at a small proportion of births, but these infants are at high risk of adverse outcomes
- Intraosseous access is included as an alternative to umbilical venous cannulation for drug administration in newborn resuscitation guidelines
- There are no clinical or preclinical trials comparing the effectiveness of intraosseous and intravenous adrenaline during newborn resuscitation

What this study adds

- Asphyxiated lambs effectively achieve return of spontaneous circulation with intraosseous adrenaline, at similar rates and administered doses, as with intravenous adrenaline
- Plasma adrenaline levels measured after intraosseous and intravenous adrenaline administration are similar, suggesting effective distribution into the intravascular space
- Given the similar physiological response, speed of access may be an important determining factor in choosing intraosseous or intravenous adrenaline in the clinical setting

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Figure Legends

Figure 1: Time to return of spontaneous circulation in intravenous (red) and intraosseous (black) lambs. Individual animals are shown with mean (95% confidence interval) included. This original figure was created by author G. R. Polglase.

Figure 2: Plasma concentration of adrenaline in intravenous (red) and intraosseous (black) lambs measured in the fetal state (F), at end asphyxia (A), and at 3 and 15 minutes after return of spontaneous circulation. Mean values are shown with error bars representing standard deviation. This original figure was created by author G. R. Polglase.

Figure 3: pH, PaO_2, $PaCO_2$, and lactate measured in arterial blood samples, and peripheral oxygenation (SpO_2), cerebral oxygenation ($SctO_2$), fraction of inspired oxygen (FiO_2) and mean airway pressure measured prior to asphyxia (control (F)), at end-asphyxia (A) and regularly after return of spontaneous circulation in lambs receiving intraosseous (IO, black) or intravenous (IV, red) adrenaline. Error bars denote standard deviation, and * indicates significant difference ($p < 0.05$). This original figure was created by author G. R. Polglase.

Figure 4: Mean blood pressure, mean pulmonary blood flow, and mean carotid blood flow measured prior to asphyxia (Control [F]), at end-asphyxia (A) and regularly after return of spontaneous circulation in lambs receiving intraosseous (IO, black) or intravenous (IV, red) adrenaline. Error bars denote standard deviation, and * indicates significant difference ($p < 0.05$). This original figure was created by author G. R. Polglase.