WORKSHEET for Evidence-Based Review of Science for Neonatal Working Group

Worksheet author(s)

Jonathan Wyllie

Date Submitted for review:

29.12.2009

Clinical question.

In neonates (P) born without discernable cardiac output or a heart rate < 60 BPM does the intravenous (I) versus the endotracheal route of adrenaline/epinephrine (C) result in improved outcome (O)? (outcome=short term physiologic, survival, intact survival)

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention

State if this is a proposed new topic or revision of existing worksheet. New version of previous worksheet

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? None

Search strategy (including electronic databases searched).

Medline(1966-2008), Embase, Cinahl, Hand searches of journals and Review articles, Cochrane Database


State inclusion and exclusion criteria

Relevant adult and pediatric studies.

Relevant animal studies involving asphyxial arrest or comparative data concerning intravenous or endotracheal administration.

Neonatal studies.

Review articles without new data were not included but were used to review references.

Number of articles/sources meeting criteria for further review:

Any Field

Adrenaline (123,159), +Infant (2027), +Resuscitation (236)+ Survival (65) = All reviewed
Adrenaline (123,159), +Newborn (2871), +Resuscitation (173)+ Survival (42) = 21 to review
Epinephrine (117965) + Newborn (2739) + Resuscitation (153) +survival (37)= 1 to review
Epinephrine (117965 + Neonatal (2038) + Resuscitation(154) +survival 37) = all were reviewed no new articles
Epinephrine (117965)+ Endotracheal (246) + Resuscitation(107) all reviewed abstracts = 28 articles to review
Epinephrine (117965)+ Endotracheal (246) + Resuscitation(107)+Survival (26) all were reviewed = 2 articles
Adrenaline () + Endotracheal (274) + Resuscitation (118) + Survival (28) all reviewed = no new papers
Adrenaline (123159)+ Endotracheal (273) + Resuscitation(117) all were reviewed = 4 new papers to review
Adrenaline (123159) + Endotracheal (273)+ Intravenous (80) all were reviewed =4 articles to review
Adrenaline (123159) + Neonatal (2147)+Survival (134) all were reviewed = 1 new articles
Adrenaline (123159) + Infant (2027) + Survival (166) all were reviewed = no new articles
Newborn (533008 ) + Endotracheal (1570)+ adrenaline(47)= no new articles
Newborn(533008 ) + Endotracheal (1570)+ epinephrine(41) = all were reviewed 1 new articles
Adrenaline+Intravenous+CPR (83) reviewed abstract = 6 new articles for further review
Adrenaline+Intravenous+Resuscitation (308) + infant (31) no new articles
Adrenaline+Intravenous+Resuscitation (308) + pediatric (22) no new articles

MeSH keywords

Newborn(424,794 ) + Endotracheal (0)+ adrenaline(0)=no new articles
Newborn(424,794) + Endotracheal (0) + epinephrine (0)=no new articles
Newborn (424,794) + Adrenlaine (721) + Resuscitation (84) all reviewed = no new articles.

98 articles reviewed, with 60 reviewed in detail and 45 included.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Barber 2006&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Chen 2006&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Crespo. 1999&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Jonmarker 1996&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Mielke, 1998</td>
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<tr>
<td>Fair</td>
<td>Hahnel 1989&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Hornchen1992&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Hornchen 1987&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Mazkereth 1992&lt;sup&gt;E&lt;/sup&gt;</td>
<td>McCrirrick 1992&lt;sup&gt;E&lt;/sup&gt;</td>
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<tr>
<td>Poor</td>
<td>Niemann 2000&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Niemann 2002&lt;sup&gt;A&lt;/sup&gt;</td>
<td>Orlowski 1990&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Pasternak1983&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Quinton 1987&lt;sup&gt;E&lt;/sup&gt;</td>
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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

*Italics = Animal studies*
### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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- **Good**
  - Schwab 1994<sup>E</sup>
  - Jasani, 1994<sup>AB</sup>
  - Jasani 1994<sup>h</sup><sup>AB</sup>
  - McCaul 2006<sup>AB</sup>

- **Fair**
  - Finer 1999<sup>ABC</sup>
  - Campbell 2004<sup>ABD</sup>
  - O'Donnell 1998<sup>ABCD</sup>
  - Sanchez-Torres, 2007<sup>ABCD</sup>
  - Thrush 1997<sup>E</sup>
  - Perlman 1996<sup>AB</sup>

- **Poor**
  - Ziino, 2003
  - Sims 1994<sup>ABCd</sup>
  - Chen 2007

**Italics = Animal studies**

### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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- **Good**
  - Lucas, 1994<sup>E</sup>
  - Chernow 1984<sup>E</sup>

- **Fair**
  - Greenberg 1979<sup>E</sup>
  - Paret 1997<sup>E</sup>
  - Raymondos 2000<sup>E</sup>
  - Thrush, 1997
  - Redding 1967<sup>E</sup>

- **Poor**
  - Lindemann 1982<sup>+</sup>
  - Lindemann 1984<sup>+</sup>
  - Jankov 2000<sup>ABCD</sup>
  - Thornberg 1995<sup>ABCD</sup>

**Italics = Animal studies**
A level 4 retrospective cohort analysis demonstrates that when adrenaline/epinephrine is used the initial route is usually endotracheal but it is successful in only 33% of cases (LOE 4 Barber 2006). IV adrenaline/epinephrine achieved ROSC in 77% of those who had failed ET treatment suggesting that this is the more effective treatment. However, 12 good and 14 fair adult or animal studies demonstrate either that the present recommended endotracheal dose has no demonstrable effect on blood pressure or survival, or that the physiological effect is much less than with intravenous administration, or that an increased dose of up to 10 times the present dose is required when delivered via the tracheal tube. Given these findings, it is tempting to assume that the 33% response in the Barber 2006 (LOE 4) study may represent survival without adrenaline/epinephrine. It is the same as the survival in the Jasani 1994 study (LOE 5) using 50 mcg/kg. Several studies have suggested that an effective ET dose will be above 50 mcg/kg (LOE 5 Chen 2006, Hornchen 1992, Hornchen 1987, Mannisterski 2002, Mazkareth 1992, McCrirrick 1994, Miekle 1998, Nieman 2000, Niemann 2002, Ralston 1985 Raymondos 2000, Yang 1991). To support this, three level 4 papers oppose the statement (Lindemann 1982; Lindemann 1984; Jankov 2000). However, two by Lindeman 1982+1984 are case series which replicate the same data and the dosage used was between 16-50 mcg/kg via ET. One by Jankov 2000, suggests good outcome for ET adrenaline but there are significant problems with this data. There are 8 adult or animal studies which are supportive of the possibility of efficacious ET administration but none at the dose presently used (LOE 5 Greenberg 1979, Hornchen 1987, Mannisterski 2002, Mazkareth 1992, Miekle 1998, Ralston 1985, Raymondos 2000, Yang 1991). Direct comparisons are limited to 8 studies (LOE 5 Jonmarker 1996, Kleinman 1999, McCrirrick 1992+1994, Mielke 1998, Niemann 2000, Orlowski 1990, Quinton 1997) which demonstrate the superiority of the intravenous route either physiologically or in terms of ROSC and survival but are animal or adult studies. One study (LOE 5 Ralston 1985) suggests that ET or IV are equivalent but with a larger dose than currently recommended for ET administration. Redding 1967 (LOE 5) showed equivalence in a non-newborn asphyxia animal model but dose was not given by weight.

There is some evidence of potential harm for adrenaline/epinephrine in rebound hypertension and tachycardia but more concerning is the increased mortality reported after administration of adrenaline/epinephrine after brief asphyxia arrest in rats (LOE 5 McCaul 2006). This is not a newborn model but in the absence of evidence for efficacy of ET adrenaline/epinephrine at the present dosages and the documented over-usage (LOE 4 O'Donnell 1998, Jankov 2000, LOE 5 Schwab 1994) it raises concerns.

Acknowledgements:

Jeff Perlman and Diane Atkins

Citation List


Comment: Present dose of adrenaline often ineffective. 77% of those who did not respond to ET adrenaline responded to IV adrenaline. IV adrenaline would seem therefore to be at least 2.6 times more effective than ET

Level of Evidence 4
Quality – Good for this subject
Evidence – Supportive of intravenous administration being more effective than ET. Supportive for increased ET dose and ineffectiveness of present dose ET


Comment: Retrospective observational study below 750g. No distinction between compressions and epinephrine at birth in the CPR group. However, all who received CPR died. Epinephrine infusion was also associated with poor outcome.

Level of Evidence 4
Quality – Fair for this subject
Evidence- Neutral.

Comments: IV gives higher blood levels in relation to ET administration even when 5 times the dose used ET. However, non-arrest model
Level of Evidence 5
Quality – Good
Evidence- Supporting.


Comments: Asphyxial model but adult animals. Epinephrine does work IV in comparison to vasopressin but this is at a very high dose. Does not address the Et route.
Level of Evidence 5
Quality – Poor for this
Evidence- Neutral.


Comments: Not an arrest model, no weights given so actual dose per kg is unclear.
Level of Evidence: 5 Against
Quality: Fair
Evidence: Against PICO as +/- Supports ET (with normal pulmonary blood flow some endotracheal drug is at least absorbed)


Comments: BP and epinephrine levels did not differ between the 0.01 mg/kg dose and no drug. 0.1 mg/kg dose caused increased drug levels but no sustained improvement in mean arterial blood pressure or diastolic BP. However it is a ventricular fibrillation model.
Level of Evidence: 5
Quality: Good
Evidence: Supportive of IV and against current endotracheal dosing recommendation


Comments: Of those babies <1500g receiving CPR, 66.7% received adrenaline/epinephrine. In favour of survival of babies after adrenaline/epinephrine but suggests that there is a progression from compressions to drugs. This is worrying due to the potential harmful effects of adrenaline/epinephrine.
Level of evidence 4
Quality: Fair
Evidence: Neutral for this question


Comment: Supportive of ET administration as effective in anaphylaxis. However, not an arrest model and dose was larger than normal.
Level of evidence 5
Quality Fair
Evidence Against statement.


Comment: Review article
Level of evidence 5
Quality Fair
Evidence Supporting statement.

Comments: Endobronchial rather than direct injection into ET tube, cardiac arrest model. Large dose at 100mcg/kg. Favours the technique which gives highest peak levels as in arrest the metabolism is increased.
Level of Evidence: 5
Quality: Fair
Evidence: Supports


Comments: Endobronchial rather than direct injection into ET tube, cardiac arrest model. ET was 10X the IV dose.
Level of Evidence: 5
Quality: Fair
Evidence: Supports use of ET route but dose is 10X that recommended by ILCOR. Therefore raises doubt as to the effectiveness of the present doses used ET


Comment: 12/16 babies who received CPR also received adrenaline (75%). There were 9 survivors and 8 showed no disability. However, adrenaline given early (range 1-15 min) in some and one patient received adrenaline before compressions and was excluded. This outcome data is different from Sims et al and even O'Donnell. There is a worry that if we give adrenaline to those who do not need it the outcome will be good.
Level of Evidence 4- Against
Quality: Poor
Evidence: Against the statement


Comments: Good model for neonates (hypoxic and hypercarbic). No difference in ROSC between groups or other outcomes therefore recommend direct injection since it is the simplest. It is a shame that an intravenous arm was not included. Asphyxial but pediatric model.
Level of Evidence: 5
Quality: Good
Evidence: Supports ET although with 50mcg/kg therefore neutral for this PICO


Comments: Good model for neonates (hypoxic and hypercarbic). No difference in ROSC between groups or other outcomes therefore recommend direct injection since it is the simplest
Level of Evidence: 5
Quality: Good
Evidence: Supports ET although with 50mcg/kg therefore neutral for this PICO


Comments: Smaller doses than currently recommended. Non-arrest paradigm.
Level of Evidence: 5 (None neonatal and not at birth)
Quality: Good
Evidence: Supportive (Epinephrine was absorbed from the airways but that absorption was unreliable).


Comments: Good randomised study in newborn term piglets. It suggests that IV administration of adrenaline(epinephrine) is more efficacious. However, there are methodological problems making extrapolation to newly born infants since the piglets were pre-ventilated and the mode of arrest was fibrillation rather than hypoxia. Unfortunately a neonatal model with induced arrest via V-fib rather than asphyxia. Did use currently recommended dose of endotracheal epinephrine.
Level of Evidence: 5
Quality: Good
Evidence: SUPPORTS


**Comments:** Case series with no control group. Often quoted as reportedly successful although one baby was not newly born. It is surprising that if these infants really needed adrenaline (epinephrine) that all resuscitations were successful. Quality control of resuscitation is an issue in an observational case series. Therefore a poor study upon which to base practice. An excellent prompt for further research.

All other reports show 1-3 minutes before response to ET tube epinephrine so was it the epinephrine that they responded to or improved ventilation? This dosage is at 16-50 mcg/kg

**Level of Evidence:** 4

**Quality:** Poor

**Evidence:** AGAINST


**Comments:** Useful paper in what it sets out to measure but once again it deals with lambs who are merely hypoxic and not in cardiac standstill; all animals had a secure airway and were ventilated. Potentially supportive of endotracheal administration as a route in profound bradycardia at birth. They used a very small dose. Model is hypoxia but would have been better to have asphyxia.

**Level of Evidence:** 5

**Quality:** Good

**Evidence:** AGAINST


**Comments:** Healthy, non-arrest model

**Level of Evidence:** 5

**Quality:** Good

**Evidence:** Supports at current recommended dose


**Comments:** Healthy, non-arrest model, used dose and diluent similar to clinical neonatal use, no positive hemodynamic effects

**Level of Evidence:** 5

**Quality:** Fair

**Evidence:** SUPPORTS as no hemodynamic effect at dose ILCOR recommends


**Comments:** This is an asphyxial but not newborn model. It raises further concerns about higher dose adrenaline as well as the risks of its use inappropriately.

**Level of Evidence 5**

**Quality –Good**

**Evidence – Neutral**


**Comments:** Non-arrest situation. Extremely small doses—much lower than current recommendations. However, IV had an effect and 5 times the dose ET did not.

**Level of Evidence:** 5

**Quality:** Fair

**Evidence:** Supportive

**Comments:** Non-arrest situation.
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Supportive


**Comments:** Well done study in adult model of non-arrest and used higher dose than is recommended by ILCOR for neonates. EVEN WITH higher ET tube epinephrine dose the peak levels are higher with iv. No disadvantage to direct injection of epinephrine compared to endobronchial.
**Level of Evidence:** 5
**Quality:** Good
**Evidence:** SUPPORTS


**Comments:** Well done study in adult model of non-arrest. No difference between ET routes but better with iv.
**Level of Evidence:** 5
**Quality:** Good
**Evidence:** SUPPORTS


**Comments:** Decreased concentrations of epinephrine reach the heart via the pulmonary circulation with decreasing age.
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Supports


**Comment:** Adult arrest
**Level of Evidence** 5 (for neonates)
**Quality of evidence-Fair**
**Evidence Supports intravenous over ET although adult arrest study**


**Comments:** Adult out of hospital arrest showing that ET adrenaline at twice the iv dose was not effective. No long term survivors for the ET adrenaline group.
**Level of Evidence** 5 (for neonates)
**Quality of evidence-Fair**
**Evidence Supports higher ET dose or that intravenous is superior to ET**


**Comment:** High rate of use of adrenaline in 1 in 500 births. Adrenaline given by ET alone in 82% of cases and 94% overall. Guidelines permitted use of compressions or adrenaline prior to establishing airway and breathing. There is a real danger with the ET route being used primarily as a way to administer adrenaline as opposed to airway control and effective ventilation. Outcome difficult to interpret when 7 babies who received adrenaline only had transient tachypnoea of the newborn. Asystole not defined and timing of adrenaline not given. Often quoted to justify adrenaline at low gestational age; however, the paper makes the case for airway and ventilation as the priorities.
**Level of Evidence** 4
**Quality Poor to Fair**
**Evidence Neutral**

**Comments:** Question whether correct statistics used—using paired t-test for 4 different comparisons per animal. However, showed variable results with ET dosage.
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Supportive


**Comments:** Non-arrest model with normal pulmonary blood flow. There was no increase in BP with Epinephrine in any treatment group, don’t show any baseline values prior to ET tube epinephrine
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Against but no increase in Blood Pressure


**Comment:** Acute onset of cerebral hypertension, as may be seen in response to catecholamines, may be significant in the reperfusion injury following cardiac arrest or in infants with IVH. Certainly suggests one should be sure of the need to use epinephrine. This study is not in agreement with data from Jankov.
**Level of Evidence 5.**
**Quality:** Fair
**Evidence:** Supports


**Comments:** Suggests that adrenaline is successful but insufficient data to decide about route.
**Level of evidence:** 4
**Quality:** Fair
**Evidence:** Neutral


**Comments:** Authors may have been biased before starting their study. Adults but asystolic arrest. No real outcome data.
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Supportive


**Comments:** CPR after only 2.5 minutes of cardiac arrest (not likely in neonates) PEA arrest and epinephrine levels were not measured. Outcomes for only 2 minutes.
**Level of Evidence:** 5
**Quality:** Fair
**Evidence:** Supports use of ET tube epinephrine but suggests that a dose much larger than the dose recommended by NRP may be needed. Therefore SUPPORTS the present statement.


**Comments:** non-arrest population. Adult aneesthesia.
**Level of Evidence:** 5
**Quality:** Fair
Evidence: Against BUT although ET tube epinephrine can cause hemodynamic effects the dose used is much larger than the current dose recommended by ILCOR


Critique
Methodology: Non-randomized or blinded with no sample size calculations. Comparison of 1 mg epinephrine via i.v. versus ET tube in 1 cc NS, versus ET tube in 10 cc NS versus ET tube in 10 cc water.
Participants: adult dogs (n=10 per group) in asphyxial arrest (5 minutes) followed by ventilation with oxygen, CPR and defibrillation if needed.
Outcomes: ROSC, development of V-fib, time to ROSC
Outcome Designation: A

<table>
<thead>
<tr>
<th>Findings</th>
<th>Route</th>
<th>ROSC</th>
<th>V-fib</th>
<th>Time to ROSC</th>
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<tbody>
<tr>
<td>i.v.</td>
<td>10/10 ROSC</td>
<td>2 V-fib</td>
<td>127 s</td>
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<tr>
<td>ETT 1mg in 1cc</td>
<td>2/10 ROSC</td>
<td>3 V-fib</td>
<td>116 s</td>
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</tr>
<tr>
<td>ETT 1 mg in 10 cc NS</td>
<td>8/10 ROSC</td>
<td>2 V-fib</td>
<td>217 s</td>
<td></td>
</tr>
<tr>
<td>ETT 1 mg in 10 cc H2O 10/10</td>
<td>ROSC</td>
<td>2 V-fib</td>
<td>132 s</td>
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Comments: Reports water is better absorbed into the lungs than saline. Need the volume to wash the medication out of the ET tube Dosage was not standardized for weight (weights not reported)
Level of Evidence:  5
Quality: Fair
Evidence: Against also shows the effectiveness of IV adrenaline


Comments: Suggests that outcomes are independent of CPR but do not define whether they were given adrenaline.
Level of Evidence:  4
Quality: Fair
Evidence: Neutral


Comments: Demonstrates that adrenaline (epinephrine) is absorbed when given endotracheally. However, there is a high use (29%) in preterm babies needing resuscitation with a low immediate mortality after its use. This raises the possibility that the population of babies did not really require the adrenaline but were merely given it. The study is therefore one of absorption rather than efficacy.
Level of Evidence 5-
Quality
Evidence Neutral


Comment: Retrospective data for 105 infants who had received epinephrine (adrenaline) and/or atropine for resuscitation. Only 21 at delivery. Of 25 survivors, 9 were severely handicapped at follow-up. Worse outcome if under 29 weeks gestation or asystole
Level of Evidence 4
Quality Poor for this question
Evidence: Neutral


Comment: Not possible to get the data from this as to the effect of adrenaline or the mode of delivery
Level of evidence 4
Quality Poor for this question
Evidence: Neutral


Comment: This is an adult model
Level of Evidence 5
Quality Fair
Evidence Neutral


Comments: Confirms that there may be a deleterious effect of low dose ET adrenaline mediated by beta-adrenergic effects lowering blood pressure. Not an arrest model or neonatal.

Level of Evidence 5
Quality of evidence - Fair
Evidence: supportive


Comments: Asphyxial arrest, used catheter beyond tip of ETT to administer drugs, underpowered to show any differences, no difference in time to onset of drug effect, ROSC, and duration of hypertension. No difference between diluents.
Level of Evidence: 5
Quality: Fair
Evidence: Supports as only useful if 10X dose recommended via ILCOR


Comments: No studies therefore neural and poor.