**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Jonathan Wyllie | Date Submitted for review: 19.10.2009 |

**Clinical question.**

In neonates (P) born without discernable cardiac output or a heart rate < 60 BPM does the intravenous (I) or the endotracheal route of adrenaline/epinephrine above the standard dosages versus the standard dosages (C) result in improved outcome (O)? (O = survival to discharge, intact neurological 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: This is a new 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(1966-2009), Embase, Cinahl, Hand searches of journals and Review articles, Cochrane Database Also used Pubmed related articles

Search criteria key words included: Adrenaline, epinephrine, neonate, newborn, paediatric/pediatric, asphyxial arrest, asphyxia, resuscitation, high dose adrenaline/epinephrine, endotracheal, tracheal, resuscitation, CPR.

- **State inclusion and exclusion criteria**

  Included relevant adult, pediatric/paediatric and animal data on adrenaline/epinephrine dosage, effect or asphyxial arrest.
  Included neonatal and infant studies as well as studies of asphyxial arrests.
  Included relevant randomized, studies, case controlled studies, case series.
  Excluded papers published only in abstract

- **Number of articles/sources meeting criteria for further review:**

  Keywords (MeSH)
  - Epinephrine/Adrenaline 106824, +Neonatal 721, +Resuscitation 84 (Reviewed)
  - Epinephrine/Adrenaline 106457, +Tracheal 412 (Reviewed abstracts), +neonate 5 or +infant 9
  - Epinephrine/Adrenaline 106824, + endotracheal 0, + pediatric/paediatric 0
  - Epinephrine/Adrenaline 106824, + asphyxia 111 (Reviewed abstracts) + resuscitation 40 or CPR 0

  Keywords (MeSH0 for first followed by any field
  - Epinephrine/Adrenaline 106824, +Neonatal (any field) 1760, +Resuscitation 109 (Reviewed).
  - Epinephrine/Adrenaline 106824, +Tracheal 636, +neonate 15 or +infant 28 (Reviewed)
  - Epinephrine/Adrenaline 106824, + asphyxia 215 + resuscitation 72 or CPR 15 (Reviewed)
  - Epinephrine/Adrenaline 106824, + endotracheal 157, + pediatric/paediatric 22 (Reviewed)

  Ultimately 49 papers were included of which there was only one level 1 paper as a systematic Cochrane review which was neutral (No randomize studies to review!). All other papers were level 4 or less.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
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<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
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<tr>
<td>Barber (ET) 2006</td>
<td>Hornchen (ET) 1994&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Vaknin (ET) 2001&lt;sup&gt;E&lt;/sup&gt;</td>
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<td>Jasani (ET) 1994&lt;sup&gt;B&lt;/sup&gt;</td>
<td>Ralston (ET) 1985&lt;sup&gt;B&lt;/sup&gt;</td>
<td>Yang (ET) 1991&lt;sup&gt;E&lt;/sup&gt;</td>
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<td>Kleiman (ET) 1999&lt;sup&gt;B&lt;/sup&gt;</td>
<td>Berkowitz 1991&lt;sup&gt;E&lt;/sup&gt;</td>
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<td>Goetting, 1989&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Crespo 1991(ET)&lt;sup&gt;E&lt;/sup&gt;</td>
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<td>Jonmaker (ET) 1996&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Lindner 1991&lt;sup&gt;AE&lt;/sup&gt;</td>
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<td>Manisterski (ET) 2002&lt;sup&gt;E&lt;/sup&gt;</td>
<td>McCirrick (ET) 1994&lt;sup&gt;E&lt;/sup&gt;</td>
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<td>Nieman (ET) 2000&lt;sup&gt;AB&lt;/sup&gt;</td>
<td>Roberts (ET) 1978&lt;sup&gt;B&lt;/sup&gt;, 1979&lt;sup&gt;B&lt;/sup&gt;</td>
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<td>Paradis 1991&lt;sup&gt;E&lt;/sup&gt;</td>
<td>Raymondos (ET) 2000&lt;sup&gt;E&lt;/sup&gt;,</td>
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## Evidence Neutral to Clinical question

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**A** = Return of spontaneous circulation  
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**E** = Other endpoint  
*Italicics* = Animal studies

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## Evidence Opposing Clinical Question

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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

This PICO should really be split into two different questions in order to address intravenous and endotracheal administration separately.


However, the evidence is all Level 5 in terms of a neonatal population, but it is difficult to see an ethics committee permitting a randomized controlled trial of high dose intravenous adrenaline/epinephrine in a clinical setting. Whilst Burchfield 1993 (LOE 5) in a newborn animal model, suggested a higher dose than 10mcg/kg may be beneficial with short term physiological outcome measures it was also shown that 100mcg/kg had potentially detrimental effects. There is experimental evidence of potential harm of high dose adrenaline/epinephrine in terms of hypertension , cortical cerebral vasoconstriction (LOE 5 Gedeborg 2000) tachycardia and mortality (LOE 5 Berg 1994, Berg 1996, McCaul 2006, Niemar 1995).

On the contrary there is evidence that the standard dose of endotracheal adrenaline is likely to be ineffective from both clinical (LOE 4 Barber 2006) and experimental studies (LOE 5 Jasani 1994, Jonmaker 1996, Kleinman 1999, Manisterski 2002, McCrirrick 1994, Mielke 1998, Niemann 2000, Orlowski 1990 , Ralston 1985, Roberts 1979, Yang 1991, ). However, the response in the a retrospective neonatal study (LOE 4 Barber 2006) and an animal model ( LOE 5 Jasani 1994) were similar. Even the sentinel paper on clinical neonatal use of endotracheal adrenaline/epinephrine used doses of 16-50 mcg/kg (LOE 4 Linderman 1984). The present dose may even be harmful, possibly lowering blood pressure (LOE 5 Vaknin 2001) without increasing survival. Most of the evidence is LOE 5 as it is from adult and experimental animal populations. It is only reasonable to make physiological extrapolation from these studies rather than outcome measures such as ROSC as the mode of arrest is often non-asphyxial.

It is not possible to recommend any particular dose other than to say that 50mcg/kg endotracheally in an animal model (LOE 5 Jasani 1994 ) achieved a similar response to 10-30 mcg/kg in the clinical setting (Barber 2006) and 100 mcg/kg endobronchially seems to be as effective as standard intravenous treatment (LOE 5 Hornchen 1987), although the plasma levels are still lower (LOE 5 Miekle 1998).

In neonatal resuscitation it is likely that the presently recommended dose for endotracheal adrenaline/epinephrine is ineffective or sub-optimal. In this setting an unproven treatment may delay effective airway management (LOE4 Jankov 2000, O'Donnell 1998) . There is little evidence of any efficacy for this route of administration, but if it is to be used it successfully, a higher, as yet unknown dose is likely to be required. Urgent research is needed to ascertain both the efficacy and appropriate dose for endotracheal administration.

Acknowledgements: All the researchers who have tried to address these issues.
Citation List


Comment: Present dose of adrenaline often ineffective. 77% of those who did not respond to ET adrenaline responded to iv adrenaline. Suggests that IV adrenaline may be effective when ET has failed.

Level of Evidence 4
Quality –good
Evidence – Supportive for increased ET dose. Supportive for IV over ET


Comments: Although high does adrenaline/epinephrine improves initial resuscitation; it had no effect on outcome taken to hospital discharge.

Level of Evidence 5 (for neonates)
Quality of evidence-Fair
Evidence Opposed


Comments: High dose adrenaline was not more effective in improving outcome at 24 hours. High dose adrenaline was associated with more adrenergic manifestations, which may have contributed to the initial higher mortality.

Level of Evidence 5
Quality –Good
Evidence - Opposing


Comments: High dose adrenaline was not more effective than standard dose adrenaline in improving outcome at 24 hours. High dose adrenaline can induce a hyperadrenergic state that includes hypertension and tachycardia.

Level of Evidence 5
Quality –Good
Evidence - Opposing


Comment: This is adult arrest from ventricular fibrillation. The study is poor data for a neonatal asphyxial arrest model therefore.

Level of Evidence 5 (for neonates)
Quality of evidence-Poor
Evidence Opposed

6. 

Comments: In this immature animal model, a dose of 10 mcg/kg/min is the optimal dose to increase LVBF and CBF. However, this is a substantial increase above the current recommended dose. Several differences in this model as compared to the asphyxiated neonate should be noted: a) the PaCO2 was controlled and ranged from 36-39 mmHg; whereas in the asphyxiated fetus the PaCO2 values are much higher; b) the pH was maintained in the normal range, whereas in the asphyxiated fetus the pH is low, and c) the haemoglobin was 8.5 g/dl, lower than normal in the fetus.

Level of Evidence 5
Quality –Fair
Evidence –Supportive


Level of Evidence 5 (for neonates)
Quality of evidence-Excellent
Evidence Opposed


Comments: Good study suggesting a higher dose than 10mcg/kg may help in this sheep model but that 100mcg.kg may be too high. No dose therefore other than 50 mcg.kg to offer. Survival not addressed.

Level of evidence: 5
Quality: Good
Evidence: Neutral to supportive


Comment: Excellent study showing 13% of high dose group had ROSC in field vs 8% of standard dose group. However, no difference in discharge from hospital and a trend towards worse neurological outcome in high dose or noradrenaline group. However, adult arrests.

Level of Evidence 5 (for neonates)
Quality of evidence-Excellent
Evidence Opposed


Comments: Retrospective study- This study failed to demonstrate benefit from high dose epinephrine therapy.

Level of Evidence 5 (for neonates)
Quality of evidence-fair
Evidence Opposed

11.

**Comments:** High dose epinephrine enhanced myocardial perfusion. However, it was associated with decreased cardiac output.

**Level of Evidence** 5  
**Quality of evidence:** Good to fair  
**Evidence Neutral**


**Comments:** A trend towards increased survival was noted in the HDE group, although this was not significant.

**Level of Evidence** 5 (for neonates)  
**Quality of evidence:** Excellent  
**Evidence Neutral**


**Comment:** This is an animal model with ventricular fibrillation as the arrest model. Therefore limited in its application to asphyxial arrest. However, the data about blood pressure is relevant with these provisos. This would suggest that increased adrenaline may be applicable through the ET tube.

**Level of Evidence** 5  
**Quality:** Fair  
**Evidence:** Supportive for ET adrenaline only.


**Comments:** Retrospective study. Overall outcome including survival was **dismal**.

**Level of evidence** 5 (for neonates)  
**Quality of evidence:** fair  
**Evidence Opposed**


**Comment:** High-dose epinephrine appears to induce vasoconstriction of cortical cerebral blood vessels resulting in redistribution of blood flow from superficial cortex.

**Level of Evidence** 5  
**Quality of evidence:** Good to fair  
**Evidence - Opposed**


**Comments:** Uncontrolled study. Poor outcome.
Level of Evidence  5 (for neonates)  
Quality of evidence-fair  
Evidence Supportive

17.  

Level of Evidence  5 (for neonates)  
Quality of evidence-Fair  
Evidence Opposed

18.  

Comments: Although HDE improved spontaneous return of the circulation, long term survival did not differ between groups. Fibrillation as cause of arrest.

Level of Evidence  5 (for neonates)  
Quality of evidence-Excellent  
Evidence Opposed

19.  

Comment: High dose (10X) seems to work endobronchially as well as standard IV dose.

Level of Evidence 5  
Quality –Good  
Evidence – Supportive for increased ET dose

20.  

Comments: Detrimental effects on cardiac function following resuscitation appear to be related to high dose epinephrine.

Level of Evidence  5  
Quality of evidence-Fair  
Evidence Opposed

21.  

Comment: 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  
Quality: Poor  
Evidence:Neutral
22.  

**Comment:** A higher dose (50mcg/kg) than currently recommended when administered ET gave 31% resuscitation rate. Method of instillation did not affect outcome.  
**Level of Evidence 5**  
**Quality –Good**  
**Evidence – Supportive for ET dose of 50 mcg/kg**

23.  

**Comment:** Non-arrest model which shows the need for increased ET dose to get similar effects. However, both Et and IV doses were higher than present recommendations.  
**Level of Evidence 5 for neonates**  
**Quality of evidence-fair**  
**Evidence Supportive for increased dose ET**

24.  

**Comments:** Physiological outcomes showed that present doses of ET adrenaline do not have any effect. IV more effective than ET.  
**Level of Evidence 5**  
**Quality –Good**  
**Evidence – Supportive for increased ET dose or cessation at the present level.**

25.  

**Comments:** 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: Neutral**

26.  

**Comment:** Improved ROSC but did not affect discharge or longer term outcome. Adult arrest with Asystole or PEA  
**Level of Evidence 5 (for neonates)**  
**Quality of evidence-Excellent**  
**Evidence: Opposed**

27.  

**Comments:** High dose adrenaline improved spontaneous return of the circulation but had no effect on outcome.
Level of Evidence 5 (for neonates)
Quality of evidence-Fair
Evidence Supportive


Comment: RCT in animals with BP as the outcome measure. ET doses needed to be at least ten times the current recommendations.

Level of Evidence 5 (for neonates)
Quality of evidence- Good
Evidence Supportive


Comment: Only 16 adults but suggests higher ET doses are needed as standard doses are ineffective.

Level of Evidence 5 (for neonates)
Quality of evidence- Fair
Evidence Supports higher ET dose


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 –Fair
Evidence – Opposing


Comment: Even at 10X the iv dose iv still gets higher peak levels.

Level of Evidence 5
Quality –Good
Evidence – Neutral or cessation of ET adrenaline


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 cessation of use

Comment: Adult arrest  
Level of Evidence  5 (for neonates)  
Quality of evidence-Fair  
Evidence Supports higher ET dose or cessation of use


Comment: The addition of bicarbonate complicates interpretation, however, increasing dose of adrenaline above 0.01mg/kg increased mortality and histological morbidity. Interesting trend towards greater survival in higher dose groups who received bicarbonate.

Level of Evidence 5  
Quality –Fair  
Evidence – Neutral to opposing


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 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


Comment: Animal model of shock. Endotracheal adrenaline not effective at 10 or 20 mcg/kg.

Level of Evidence 5  
Quality –Fair  
Evidence – Neutral to opposing. Possibly in favor of higher ET dose


Comments: This was only after two standard doses and measured physiological markers not actual outcome.

Level of Evidence 5 (for neonates)  
Quality of evidence-Poor  
Evidence Supportive


* Randomized clinical study
Level of Evidence  5 (for neonates)
Quality of evidence-Excellent
Evidence Opposed

39.

Level of Evidence 5
Quality –Good
Evidence – Supportive for increased ET dose

40.

Comment: Adult model showing that 100 times the iv dose gave higher adrenaline levels than when using an
intravenous route.

Level of Evidence  5 (for neonates)
Quality of evidence-Poor
Evidence Supportive of higher dose ET

41.
by the intravenous and endotracheal routes." Jacep 7(7): 260-4.

Comment: Dosage only no outcome data.

Level of Evidence 5
Quality –fair
Evidence – Supportive for increased ET dose

42.

Comments: Blood levels ET were 1/10\textsuperscript{th} of those achieved IV for similar doses.

Level of Evidence 5
Quality –fair
Evidence – Supportive for increased ET dose

43.

Comment: High dose epinephrine does not improve the quality of post-cardiac arrest brain recovery during the first 3 h
of reperfusion

Level of Evidence  5
Quality of evidence-Good
Evidence. Opposed

44. *

Comments: High dose epinephrine was not associated with improved survival or neurologic outcome in adults with
cardiac arrest.

Comments: Epinephrine increased the severity of post-resuscitation myocardial dysfunction and decreased the duration of survival.


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.


Comment: Meta-analysis showing no advantage to high dose adrenaline.


Comments: ET administration less effective at increasing haemodynamic indices.


Comment: No studies to include therefore poor evidence. No randomised studies of dose or route of administration.