**Treatment of Systemic Hypotension in Preterm Infants**

*Professor Pak C. Ng*

*Department of Paediatrics*

*Prince of Wales Hospital, Chinese University of Hong Kong*

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**Definition**

- Mean systemic BP of less than an infant’s gestational age in completed weeks
- Mean BP < 10th centile with respect to birth weight and postnatal age
- Other reference charts

*Joint Working Party BAPM and RCP. Arch Dis Child 1992;67:1221-7*


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**Mechanisms**

- **Low blood volume**
  - Oedematous ill infants loss fluid into subcutaneous tissues or lungs
  - High transsepidermal water loss
  - Blood removed for biochemical and haematological analysis
  - Haemorrhage

- **Myocardial depression** (hypoxia and acidemia → myocardial depression → ↓ cardiac output)

- **Hormonal insufficiency** - cortisol
**Mechanisms**

- **High positive pressure ventilation (IPPV and HFOV)**
  - compromising venous return $\rightarrow$ ↓ cardiac output
  - splinting of the heart by hyperinflated lungs (external compression)
  - obstructing pulmonary vasculature $\rightarrow$ ↑ R ventricular volume $\rightarrow$ compresses on L ventricular cavity $\rightarrow$ ↓ L ventricular output

- **Others**
  - hypothermia
  - birth asphyxia
  - infection
  - cardiac problems e.g., PDA, hypoplastic left heart
  - vascular tone deficiency
  - chorioamnionitis / funisitis (early-onset hypotension)
  - drugs e.g., morphine

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**Hypotension**

$\downarrow$ BP $\rightarrow$ ↓ intravascular volume
- myocardial dysfunction
- ↓ vascular tone, etc
$\downarrow$
$\downarrow$
$\downarrow$
$\downarrow$
$\downarrow$

**inadequate tissue perfusion**

$\downarrow$

hypoxia and acidaemia

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**Adverse outcomes of hypotension**

Many studies have shown that sustained hypotension and hypoxaemia in preterm infants resulted in substantial ↑ in major brain abnormalities such as:

- hyperechoic parenchymal lesions
- intraventricular haemorrhage
- ventriculomegaly

(53% in hypotensive vs 8% in non-hypotensive infants)

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**Adverse outcomes of hypotension**

- retrospective review; n = 110
- ELBW (400 – 999 g) infants
- comparing infants with ‘treated hypotension’ (i.e., volume expanders, inotropes and corticosteroids) at the first 72 h of life vs those with no hypotension
  - neurodevelopment testing and Bayley assessment
  - multivariate analysis adjusted for socioeconomic status and neonatal morbidity
- ‘treated hypotension’ infants were more likely to have delayed motor development, hearing loss and death

Treatment of hypotension in preterm infants

- **Volume replacement** (blood, crystalloids, colloids)
- **Inotropes** (dopamine, dobutamine, adrenaline)
- **Hormone replacement therapy** (hydrocortisone or dexamethasone)

Inotropes vs Volume expansion

Often difficult to distinguish:

Hypovolaemia vs Myocardial dysfunction

(and both factors may co-exist)

Inotropes vs Volume expansion

- RCT, n = 39, sealed envelopes
- VLBW infants
- 20 ml/kg of plasma protein fraction (PPF) may be given for initial resuscitation
- 4.5% albumin (n = 20) vs dopamine (n = 19)
  - 20 ml/kg over 30 min
  - repeated 2nd dose after 30 min
  - 9/20 (45%) received PPF initially
  - 9/20 (45%) responded
  - 10/19 (53%) had PPF initially
  - 17/20 (89%) responded
- because a significant proportion of patients were resuscitated with PPF, the study only demonstrated that infants who subsequently developed hypotension were likely to have myocardial dysfunction


Treatment of low blood volume

Blood transfusion

- especially in infants with Hct < 0.40 or Hb < 12-13 g/dL
- packed cells (15 - 20 ml/kg, over 30-120 min depending on clinical condition)

Caution

- infants with poor cardiac function may not tolerate sudden ↑ in volume expansion
- ? hepatic iron deposition with repeated blood transfusions
**Fluid volume vs Protein load**

- RCT, n = 60
- preterm infants
- 20% albumin (n=20) vs FFP (n=20) vs 4.5% albumin (n=20)
  - 5 ml/kg
  - 15 ml/kg
  - 15 ml/kg
  - infusion rates were 5 ml/kg/h in all groups
- mean ↑ in BP 1 h after the infusion, was significantly lower in infants receiving 20% albumin (i.e. 9% ↑ in 20% albumin vs 19% ↑ in FFP vs 17% ↑ in 4.5% albumin)
- the volume infused rather than albumin load is more important in producing a sustained ↑ in BP

*Emery et al. Arch Dis Child 1992;67:1185-8*

**Colloids vs Crystalloids (Adults)**

- meta-analysis
- 37 RCTs with 1622 patients
- resuscitation with colloids were associated with an increased risk of mortality (4 extra deaths for every 100 patients resuscited)

*Schierhout and Roberts. BMJ 1998;316:961-4*

**Colloids vs Crystalloids (All groups)**

- meta-analysis
- 105 articles reviewed in which 17 (814 critically ill patients) were selected
- no overall differences in:
  - pulmonary oedema
  - mortality
  - duration of hospital stay
- subgroup analysis revealed that isotonic crystalloid resuscitation is associated with a lower mortality in trauma patients

*Choi et al. Crit Care Med 1999;27:200-9*

**Colloids vs Crystalloids (Adults)**

- meta-analysis
- 30 RCTs with 1419 critically ill patients
- the risk of death in the albumin treated group was higher than in the crystalloid group
- for every 100 patients treated with albumin, there are 6 additional deaths

Proposed mechanisms:

- **Anticoagulant properties:**
  - inhibiting platelets aggregation
  - enhancing inhibition of Factor Xa by antithrombin III
    may be detrimental to critically ill patients with
    haemorrhagic hypovolaemia
- **Albumin leaks** across the capillary membrane into the extravascular spaces and results in worsening oedema

Colloids vs Crystalloids (Preterm infants)

- **RCT, n = 63**
- gestations: 23-34 wks; BW:540-1950g
- Normal saline (n = 31) vs 5% albumin (n = 32)
  - 10 ml/kg of the test solution
  - a total of 3 infusions (i.e. .30 ml/kg)
- no difference in outcome as assessed by:
  - no. of infants requiring subsequent inotropic support
  - chronic lung disease
  - death
- 5% albumin group
  - required significantly more volume expander to maintain a normal BP
    (median 27.5 ml/kg vs 10 ml/kg)
  - had high mean % weight gain within the first 48 h
- normal saline was as effective as 5% albumin for treating hypotension BUT it is much cheaper and caused less fluid retention

So et al. Arch Dis Child 1997;76:F43-6

Colloids vs Crystalloids vs Hydroxyethyl starch

- **RCT, n = 21**
- gestations: 29 (± 3) wks

<table>
<thead>
<tr>
<th></th>
<th>Normal saline</th>
<th>5% albumin</th>
<th>Hydroxyethyl starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic flow</td>
<td>0.03 (-0.03 to 0.12)</td>
<td>0.05 (-0.02 to 0.07)</td>
<td>0.03 (-0.04 to 0.11)</td>
</tr>
<tr>
<td>velocity (m/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>after 10 min of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infusion (p = 0.79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP normalization (%)</td>
<td>57% (20 - 94%)</td>
<td>86% (60 - 100%)</td>
<td>71% (37 - 100%)</td>
</tr>
<tr>
<td>(p = 0.50)</td>
<td></td>
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</tr>
</tbody>
</table>

- no evidence that hydroxyethyl starch was superior


Dopamine vs Dobutamine

- **case series, n = 12**
- preterm infants
- all 12 infants responded when the infusion rate was 10 µg/kg/min
- dobutamine failed to raise the mean BP in 7 who relapsed
- recommended to start dopamine at a rate of 10 µg/kg/min in order to avoid delay in treatment

**(Dopamine vs Dobutamine)**

- RCT, n = 40
- gestational age: 23-33 wks
- patients with hypotension despite colloid expansion
- dopamine (n = 20) vs dobutamine (n = 20)
  - starting dose 5 µg/kg/min
  - increased over 3 h to 15 µg/kg/min
- infants receiving dopamine had significantly higher median systolic BP (39 mmHg vs 34 mmHg in the dobutamine group)

*Greenough and Emery. Eur J Pediatr 1993;152:925-7*

**(Dopamine vs Dobutamine)**

- RCT, n = 20
- gestational age < 32 wks
- dopamine (n = 10) vs dobutamine (n = 10)
  - starting dose 5 µg/kg/min
  - increased in increment of 5 µg/kg/min
  - maximum rate of 20 µg/kg/min
- all 10 infants were successful in achieving BP ≥ 31 mmHg after treatment with dopamine, whereas 6 of 10 infants failed in the dobutamine group

*Roze et al. Arch Dis Child 1993;69:59-63*

**(Dopamine vs Dobutamine)**

- RCT, n = 63
- gestational age ≤ 34 wks with RDS
- dopamine (n = 31) vs dobutamine (n = 32)
  - starting dose 5 µg/kg/min
  - increased in increments of 5µg/kg/min
  - maximum rate of 20 µg/kg/min
- no infants in the dopamine group failed to maintain a BP ≤ 30 mmHg after treatment, whereas 5 of 32 infants (16%) failed in the dobutamine group
- the increase in mean arterial BP was significantly higher in the dopamine group (11.3 mmHg vs 6.8 mmHg)


**Inotropes**

Dopamine has been shown to be more effective than dobutamine in raising blood pressure in neonates

*Short et al. Pediatrics 2006;117:S34-9*
Dopamine vs Adrenaline

- RCT, n = 60
- gestations < 32 weeks; BW < 1,501 g

<table>
<thead>
<tr>
<th>Dose (µg/kg/min)</th>
<th>Dopamine (n = 28)</th>
<th>Adrenaline (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increment</td>
<td>↑ stepwise every 20 min</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Withdrawal of inotropes</td>
<td>66 (±28) h*</td>
<td>38 (±20) h</td>
</tr>
<tr>
<td>Insulin usage</td>
<td>12%</td>
<td>45%*</td>
</tr>
</tbody>
</table>

- other medium term outcomes e.g. PDA, BPD, NEC, GI complications, sepsis, severe ROP and mortality were not significantly different between groups
- Conclusions: dopamine (low/moderate dose) was as effective as adrenaline (low-dose) for treatment of hypotension in VLBW infants BUT adrenaline was associated with more transient adverse effects


HPA axis

- hypothalamus, pituitary and adrenal glands are dynamic endocrine organs during fetal development
- adrenal glands, in particular, exhibit remarkable transformation in size, morphology and function during the perinatal and early neonatal periods

Mesiano and Jaffe. Endocr Rev 1999
Ng. Arch Dis Child 2000

HPA axis

Normal development of the hypothalamic-pituitary-adrenal (HPA) axis is essential for:

- regulation of intrauterine homeostasis
- influences the timing of parturition
- timely differentiation and maturation of vital organ systems

Mesiano and Jaffe. Endocr Rev 1999
Ng. Arch Dis Child 2000
Adrenocortical insufficiency of newborns

• no evidence of clinical adrenocortical insufficiency in term infants, despite dramatic remodeling of the adrenal cortex immediately after birth

• ill and extremely premature infants (< 1000 g) may have decreased ability to produce adequate amount of glucocorticoids

HPA axis immaturity

Elevated steroid precursors in preterm infants, including:

• ↑17-hydroxypregnenolone
• ↑17-hydroxyprogesterone (17-OHP)
• ↑dehydroepiandrosterone (DHEA)

+ low serum cortisol levels in stressed sick preterm infants

↓ indicating immaturity of adrenal enzyme activity and inadequate adrenal reserve for stress

Lee et al. J Clin Endocrinol Metab 1989
**HPA axis immaturity**

VLBW infants, < 32 weeks gestation (n = 67)

↓

low circulating basal ACTH and cortisol levels

↓←

1-24 ACTH test (0.1 µg/kg)

only 36% responded to ACTH stimulation

(serum cortisol < 414 nmol/L or 15 µg/dL)

↑

↑ 11-deoxycortisol / cortisol ratio

↓

suggests delayed maturation of adrenal enzyme

(↓ 11β-hydroxylase activity)

↓

physiologically inadequate circulating cortisol in stressed VLBW infants

*Korte et al. J Pediatr 1996*

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**Corticosteroids (Animal studies)**

1. significant ↑ in mean arterial pressure during cortisol infusion in preterm ovine fetuses


2 (a) an association between early cardiovascular dysfunction and impaired urinary cortisol excretion in premature baboons, and

(b) a significant improvement in cardiovascular function 4-6 h after hydrocortisone replacement

*Yoder et al. Pediatr Res 2002*

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**Refractory hypotension in preterm infants**

- very preterm (< 28 gestation weeks)
- extremely low birth weight infants (< 1000 g)
- severe hypotension
- occurs within the first week (days) of life
- refractory to conventional treatment of volume expansion and inotropic support
- responds readily to systemic corticosteroids (hydrocortisone and dexamethasone) treatment
- suspects to have ‘adrenocortical insufficiency’ (with intact pituitary function)

*Helbock et al. Pediatrics 1993
Ng et al. Arch Dis Child 2001
Seri et al. Pediatrics 2001*

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**Results (Adrenal)**

**Cortisol and inotropes or volume expanders**

Basal and peak serum cortisol at day 7 were *negatively* associated with:

- dopamine (maximum and total cumulative dose)
- dobutamine
- adrenaline
- volume of crystalloid
- duration of inotropic support
Results

Multivariate analysis (generalised additive model)

Basal and peak serum cortisol remained significantly associated with:

- the lowest systolic, mean and diastolic BP (p < 0.0001)
- duration of inotropic support (p < 0.05)

RCT

Preterm 28 weeks gestation (median), BW 690 g (median)
severe hypotension requiring adrenaline
(on day 2)

<table>
<thead>
<tr>
<th>dexamethasone (0.25 mg/kg)</th>
<th>saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 8</td>
<td>n = 9</td>
</tr>
</tbody>
</table>

adrenaline infusion was discontinued within 12 h in:
- 5 of 8 infants
- 1 of 9 infants

rescue dexamethasone
5 of 8 infants weaned off adrenaline 1-7 h later

Ng et al. Arch Dis Child 2004

Table 3: Pericentral table of serum cortisol concentrations at day 7 in preterm infants with "normal" blood pressure (Group 1) and hypotensive infants requiring inotropic support (Group 2).

<table>
<thead>
<tr>
<th>Group 1 (n = 54)</th>
<th>Group 2 (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precocity</td>
<td>0 min</td>
</tr>
<tr>
<td>7th</td>
<td>99</td>
</tr>
<tr>
<td>50th</td>
<td>142</td>
</tr>
<tr>
<td>95th</td>
<td>206</td>
</tr>
<tr>
<td>10th</td>
<td>311</td>
</tr>
<tr>
<td>50%</td>
<td>470</td>
</tr>
<tr>
<td>90%</td>
<td>602</td>
</tr>
<tr>
<td>99%</td>
<td>979</td>
</tr>
</tbody>
</table>

Results are serum cortisol concentrations (nmol/L).

RCT of prophylactic hydrocortisone for prevention of hypotension in ELBW infants

<table>
<thead>
<tr>
<th>RCT</th>
<th>HC group (n = 16)</th>
<th>Placebo group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Received vasopressors at 24 h</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Received vasopressors at 48 h</td>
<td>7%</td>
</tr>
</tbody>
</table>

Note: 3 infants in the placebo group received dobutamine
Note: 1 infant in the HC group had gastric perforation on day 6

Conclusions: prophylactic hydrocortisone treatment reduced the use of vasopressors for treatment of hypotension

Efird et al. J Perinatol 2005

RCT of a ‘stress-dose’ of hydrocortisone for rescue treatment of refractory hypotension in preterm infants

RCT
Infants with refractory hypotension
≥ 30 ml/kg isotonic saline
≥ 10 µg/kg/min dopamine
(n = 48)

HC group
(n = 24)
Placebo group
(n = 24)

Weaned off vasopressor after 72 h of treatment
19 (79 %) 8 (33 %) (p = 0.001)

Median duration of vasopressor support
39 (28-64) h 81 (47-136) h (p = 0.001)

Use of ≥ 2 vasopressors
2 11 (p = 0.009)
Use of dopamine
↓↓ - (p < 0.001)
Use of dobutamine
↓↓ - (p = 0.002)
Use of volume expanders
↓ - (p = 0.022)
Mean arterial BP
↑↑ - (p = 0.001)

Note: no spontaneous gastrointestinal perforation in either group, despite 80% of patients received prophylactic indomethacin treatment, and routine prophylactic proton pump inhibitor was given in all enrolled patients

Note: median [cortisol] < 115 nmol/L (4.17 µg/dL) or < 10th percentile

Note: HC-treated infants had significantly more glycosuria (p = 0.029)

Conclusions:
1. a ‘stress-dose’ of hydrocortisone was effective for treating refractory hypotension and TAP
2. decreased the use of vasopressors and volume expanders for BP support
3. ? proton pump inhibitor for prevention of GI perforation

Ng et al. Pediatrics 2006

Low-dose dexamethasone for treatment of refractory hypotension (retrospective study)

• retrospective study; n = 24
• gestations: 26 (23 – 34) wks; BW: 801 (457 – 1,180 g)
• refractory hypotension
  – after volume resuscitation
  – combined dopamine and dobutamine > 30 µg/kg/min
• low-dose dexamethasone:
  0.1 mg/kg → 0.05 mg/kg every 12 h for 5 doses
• Results
  – BP responded 2 h after drug administration from 30 (± 5) mmHg to 34 (± 6) mmHg
  – inotrope requirement ↓ 6 h after treatment from 34 (± 9) to 24 (± 13) µg/kg/min
  – urine output increased in the first 6 h of treatment
• Conclusions: low-dose dexamethasone rapidly ↑ BP and ↓ inotrope requirement in VLBW infants

Noori et al. Biol Neonat 2006;89:82-7
Inhaled corticosteroids on systemic BP (RCT)

RCT for RDS (data extracted from previous RCT)
- inhaled fluticasone (500 µg every 12 h)

IF group (n = 53)
Placebo group (n = 26)

<table>
<thead>
<tr>
<th>Use of volume expanders</th>
<th>↓↓</th>
<th>-</th>
<th>(p = 0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of dopamine</td>
<td>↓↓</td>
<td>-</td>
<td>(p = 0.10)</td>
</tr>
<tr>
<td>Post-treatment cortisol</td>
<td>↓↓</td>
<td>-</td>
<td>(p &lt; 0.001)</td>
</tr>
</tbody>
</table>

**Conclusion**: IF-treated infants required significantly less volume expanders (and also a trend for less inotropes usage) for BP support

*Ng et al. Biol Neonate 2004*

Mechanisms

- Corticosteroids have the ability to ↑ the density of β-adrenergic receptors within a few hours of drug administration
- Corticosteroids can reverse the desensitisation effect of prolonged catecholamine exposure on the receptors
- Corticosteroids can ↑ angiotensin 2 (type 1) receptor gene expression of the myocardium

*Davies and Lefkowitz: J Clin Endocrinol Metab 1980*
*Broddie et al. Eur Heart J 1989*
*Segar et al. Pediatr Res 1995*

Postnatal steroid survey

- Retrospective survey of cohorts
- California Perinatal Quality Care Collaborative - via Verment Oxford Network data (expanded data)
- 1,401 VLBW infants representing about one-third of the cohort

**Results**:
- Postnatal corticosteroids were used in 19.3% of infants
  - BPD (3.6%)
  - Non-BPD e.g., hypotension, stridor, etc (11.8%)
  - Both BPD and non-BPD indications (4%)
- Postnatal corticosteroids used exclusively for hypotension had
  - ↑ IVH
  - ↑ PVL
  - ↑ mortality
  - Compared with those treated for BPD or did not receive the treatment

**Conclusions**:
- Prospective studies evaluating long-term benefits are warranted

*Finer et al. Pediatrics 2006;117:704-13*

Conclusions (TAP and BP)

- Characterised the endocrinological abnormalities of ‘Transient Adrenocortical insufficiency of Prematurity’ (TAP) in hypotensive preterm infants:
  - Normal or exaggerated pituitary response
  - Adrenocortical insufficiency (within the first week)
  - Good recovery of adrenal function by day 14
- Demonstrated a significant relation between serum cortisol and BP (positive) or inotropes/volume expanders (negative) at day 7
- Provided percentiles for serum cortisol concentrations at day 7 in preterm infants with normal blood pressure and hypotensive infants requiring inotropic support
- A short course of corticosteroids is probably justified in patients with refractory hypotension
- Long-term follow-up data are urgently needed for corticosteroids treatment of hypotension