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[Intervention Review]

Corticosteroids for treating hypotension in preterm infants

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ABSTRACT

Background

Systemic hypotension is a relatively common complication of preterm birth and is associated with periventricular haemorrhage, periventricular white matter injury and adverse neurodevelopmental outcome. Corticosteroid treatment has been used as an alternative or an adjunct to conventional treatment with volume expansion and vasopressor/inotropic therapy.

Objectives

To determine the effectiveness and safety of corticosteroids used either as primary treatment of hypotension or for the treatment of refractory hypotension in preterm infants.

Search methods

Randomized or quasi-randomised controlled trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2011), MEDLINE (1996 to Jan 2011), EMBASE (1974 to Jan 2011), CINAHL (1981 to 2011), reference lists of published papers and abstracts from the Pediatric Academic Societies and the European Society for Pediatric Research meetings published in Pediatric Research (1995 to 2011).

Selection criteria

We included all randomised or quasi-randomised controlled trials investigating the effect of corticosteroid therapy in the treatment of hypotension in preterm infants (< 37 weeks gestation) less than 28 days old. Studies using corticosteroids as primary treatment were included as well as studies using corticosteroids in babies with hypotension resistant to inotropes/pressors and volume therapy. We included studies comparing oral/intravenous corticosteroids with placebo, other drugs used for providing cardiovascular support or no therapy in this review.

Data collection and analysis

Methodological quality of eligible studies was assessed according to the methods used for minimising selection bias, performance bias, attrition bias and detection bias. Studies that evaluated corticosteroids (1) as primary treatment for hypotension or (2) for refractory hypotension unresponsive to prior use of inotropes/pressors and volume therapy, were analysed using separate comparisons. Data were analysed using the standard methods of the Neonatal Review Group using Rev Man 5.1.2. Treatment effect was analysed using relative risk, risk reduction, number needed to treat for categorical outcomes and weighted mean difference for outcomes measured on a continuous scale, with 95% confidence intervals.

Main results

Four studies were included in this review enrolling a total of 123 babies. In one study, persistent hypotension was more common in hydrocortisone treated infants as compared to those who received dopamine as primary treatment for hypotension (RR 8.2, 95% CI 0.47 to 142.6; RD 0.19, 95% CI 0.01 to 0.37). In two studies comparing steroid versus placebo, persistent hypotension (defined as a continuing need for inotrope infusion) was less common in steroid treated infants as compared to controls who received placebo for refractory hypotension (RR 0.35, 95% CI 0.19 to 0.65; RD -0.47, 95% CI - 0.68 to - 0.26; NNT = 2.1, 95% CI 1.47, 3.8). There were no statistically significant effects on any other short or long-term outcome. A further two studies that have only been published in abstract form to date, may be eligible for inclusion in a future update of this review.

Authors' conclusions

Hydrocortisone may be as effective as dopamine when used as a primary treatment for hypotension. But the long term safety data on the use of hydrocortisone in this manner is unknown. Steroids are effective in treatment of refractory hypotension in preterm infants without an increase in short term adverse consequences. However, long term safety or benefit data is lacking. With long term benefit or safety data lacking steroids cannot be recommended routinely for the treatment of hypotension in preterm infants.

PLAIN LANGUAGE SUMMARY

Corticosteroids for treating hypotension in preterm infants

It is unclear whether giving steroids to premature newborn babies who have hypotension (low blood pressure) is safe and effective. Low blood pressure is a relatively common problem in premature newborn babies and has been linked with serious short and long term problems including death and neurodisability. Various treatments are used to support the circulation and boost blood pressure. One such treatment is the use of steroid drugs. This review found four small studies that evaluated the effect of steroids on low blood pressure in premature infants. At present, there is insufficient information on which to base recommendations about the value of giving steroids to babies born before term who have low blood pressure.

BACKGROUND

Systemic hypotension is a relatively common complication of prematurity, affecting approximately one-third of very low birth weight infants. It is associated with an increased risk of intraventricular haemorrhage, periventricular white matter injury and adverse long-term neurodevelopmental outcome (Miall-Allen 1987; Goldstein 1995; Cunningham 1999; Martens 2003; Kuint 2009). Current treatment of hypotension in the premature infant includes the use of volume expansion, inotropes and vasopressor agents. Corticosteroids are generally reserved for infants with refractory hypotension.

There is no widely accepted definition of hypotension, or appropriate organ perfusion pressure in the preterm infant. Hypotension is often defined in terms of a mean blood pressure (BP) below the 5th or 10th centile of a birth weight and age-specific reference range created from a sample of stable, 'healthy' preterm neonates (Cunningham 1999; Lee 1999). A frequently used alternative 'rule of thumb' defines hypotension as mean BP below the gestation (in completed weeks) of an infant, although the origin of this definition is unclear. In other neonatal units, mean BP below 30 mm Hg would be considered sub-optimal (Miall-Allen 1987).

Blood pressure is the product of cardiac output and systemic vascular resistance. The majority of hypotensive preterm babies have normal or high cardiac output, suggesting that in these circumstances hypotension is the result of low systemic vascular resistance due to either a haemodynamically significant ductal shunt or abnormal regulation of vasomotor tone (Kluckow 1996; Pladys 1999).

Several lines of evidence support a role for corticosteroids in the treatment of hypotension in preterm infants. Relative or absolute adrenocortical insufficiency is increasingly recognised as a cause of hypotension in the preterm infant (Watterberg 2002). Sick preterm infants have lower cord blood cortisol concentrations and a limited ability to increase cortisol production in response to stressful conditions. Cortisol concentrations are inversely related to gestational age and are particularly low in hypotensive infants receiving inotropic support (Scott 1995).

Glucocorticoids increase beta-adrenergic receptor expression in the cardiovascular system, increase responsiveness to circulating catecholamines and may, therefore, increase vascular tone and/or myocardial contractility (Sasidharan 1998). Exposure to antenatal corticosteroids is associated with a reduction in the need for blood pressure support in extremely low birth weight infants (Moise 1995). There are also several reports from uncontrolled case series supporting the efficacy of postnatal corticosteroids for pressor-resistant hypotension (Seri 2001).

However, a direct toxic effect of corticosteroids on the developing central nervous system is of particular concern. Current evidence suggests that early postnatal corticosteroid treatment for prevention of preterm chronic lung disease may be associated with an increase in neurodevelopmental impairment (Halliday 2010). Other potential adverse effects include increased rate of sepsis (mainly fungal), growth failure, gastrointestinal haemorrhage/perforation and hyperglycaemia (Sasidharan 1998).

OBJECTIVES

Primary:

In preterm infants with hypotension, does the use of corticosteroids (1) as primary treatment or (2) for refractory hypotension, raise blood pressure and reduce mortality and morbidity?

Secondary:

Are there any other adverse effects or benefits to the preterm infant when corticosteroids are used to treat preterm hypotension? Are there certain sub-groups of infants in whom corticosteroid therapy for hypotension is particularly effective or harmful?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials comparing oral/intravenous corticosteroid therapy with placebo, other drug or no treatment in hypotensive preterm infants.

Types of participants

Participants will be preterm infants (< 37 weeks gestation) and less than 28 days old, who have hypotension.

No birthweight or lower gestational age limits.

No specific definition of hypotension required for inclusion; this is as defined in individual studies. Studies using corticosteroids as primary treatment were included as well as studies using corticosteroids in babies with hypotension resistant to inotropes/pressors and volume therapy.

Types of interventions

Oral or intravenous corticosteroid therapy versus placebo, other drug used for providing cardiovascular support (e.g. inotrope) or no therapy.

Age range at initiation of corticosteroid therapy < 28 days.

Trials not limited in terms of dose, duration or type corticosteroid used.

Types of outcome measures

Primary outcome measures

1. Mortality (at 28 days of age, hospital discharge and long term mortality at two years of age).
2. Long term neurodevelopmental outcome (cerebral palsy, developmental delay, sensorineural impairment, abnormal neurological examination).
3. Adverse neuroradiological sequelae (all intraventricular haemorrhage [Grade 1 - 4, Papile 1978], severe intraventricular haemorrhage [Grade 3 - 4], periventricular leukomalacia).
4. Short term haemodynamic changes (treatment failure i.e. failure to increase BP to a predetermined threshold, increase in BP, increase in cardiac output).

Secondary outcome measures

1. Other morbidities: Chronic lung disease (oxygen requirement at 28 days of age; oxygen requirement at 36 weeks postmenstrual

age), retinopathy of prematurity (stage 1 - 4; requiring cryo/laser therapy), necrotising enterocolitis.

2. Adverse effects of steroid therapy (hyperglycaemia, sepsis (bacterial or fungal), gastrointestinal haemorrhage, gastrointestinal perforation, hypertrophic cardiomyopathy).

Search methods for identification of studies

See: Neonatal Group search strategy

The standard methods of the Cochrane Neonatal Review Group were used.

The following electronic databases were searched:

The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2011)

MEDLINE/PubMed, 1966 to January 2011

EMBASE 1974 to January 2011 CINAHL 1981 to January 2011

Search strategies for The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and CINAHL were developed using index terms "infant, premature", "infant low birth weight", "blood pressure", "corticosteroid", "steroid", "hydrocortisone", "prednisolone", "dexamethasone", "beclomethasone", "inotropes", "dopamine", "adrenocorticoids" and "adrenal cortical hormones". The abstracts of the annual Pediatric Academic Societies meetings from 1995 to present were searched. Original papers were retrieved and read as required. Papers with an English abstract, written in any language, that looked relevant, were retrieved and translated. Cited references from retrieved articles were searched for additional studies. Abstracts and letters to the editor were reviewed to identify randomised controlled trials which had not been published. If a randomised controlled trial was identified, the primary investigator was contacted directly to obtain further data. Editorials, indicating expert opinion, were reviewed to identify and ensure that no key studies were missed for inclusion in this review.

Data collection and analysis

Two review authors (HI and IS) independently assessed and selected the studies to be included in the review. The methodological quality of each trial was assessed by each review author using the criteria of the Cochrane Collaboration, focusing on concealment of allocation, blinding of the intervention, completeness of follow-up and blinding of the outcome assessors. Data was independently extracted by each review author. If disagreement arose on the suitability of a trial for inclusion in the review or its quality, a consensus was to be reached between all three review authors by discussion.

Analysis

Studies which evaluated corticosteroids (1) as primary treatment for hypotension or (2) for hypotension unresponsive to prior use of inotropes/pressors and volume therapy, were analysed using separate comparisons. Separate analyses were conducted for each outcome. Analysis was performed on the basis of intention to treat. The data was analysed using the standard methods of the Neonatal Review Group. Treatment effect was analysed using relative risk, risk reduction, number needed to treat (NNT) for categorical outcomes and weighted mean difference for outcomes measured on a continuous scale, with 95% confidence intervals.

Meta-analysis, if appropriate, was to be carried out using a fixed effect model. Heterogeneity between studies was to be formally examined using the I^2 statistic.

Subgroup analysis based on birth weight (< 1000 g and ≥ 1000 g, gestational age (≤ 28 weeks, > 28 weeks) type of corticosteroid, dose, route of administration and duration of treatment was to be carried out if appropriate.

All analyses were performed using Rev Man 5.1.2 software.

RESULTS

Description of studies

Included Studies

Four studies were identified as meeting the criteria for inclusion in the review (Bourchier 1997; Gaissmaier 1999; Ng 2006; Hochwald 2010). Details of these studies are given in the table 'Characteristics of included studies'.

1. Bourchier 1997

This single centre, randomised trial of 40 infants investigated the effectiveness of hydrocortisone versus dopamine in the primary treatment of hypotension. Hypotension was defined as a mean arterial pressure (MAP) of less than 25 mmHg (for babies with a birth weight of 500 to 749 g), less than 30 mmHg (babies with a birth weight of 750 to 999 g), less than 35 mmHg (babies with a birth weight of 1000 to 1499 g) on two occasions, 30 minutes apart. The method of blood pressure measurement was not specified. The intervention groups were given hydrocortisone (2.5 mg/kg, four - six hourly for 48 hours, followed by 1.25 mg/kg six hourly for 48 hours, and then 0.625 mg/kg for a further 48 hours before stopping treatment) or dopamine (5 to 20 micrograms/kg/minute). Concurrent treatment with volume expansion was permitted in both groups. Approximately one-third of the babies had been exposed to antenatal steroids and all had received prior treatment with a volume expander. Babies with a clinically significant patent ductus arteriosus were excluded.

Twenty-one babies received hydrocortisone and 19 received dopamine. The primary outcome measure was persisting hypotension despite treatment; other outcomes included survival and a range of neonatal complications (e.g. sepsis, intraventricular haemorrhage and bronchopulmonary dysplasia). Baseline plasma cortisol levels, their relationship with BP response and change with hydrocortisone/dopamine therapy were also examined.

2. Gaissmaier 1999

This small study of 17 infants assessed the effectiveness of dexamethasone given to preterm infants with refractory hypotension. The design was a single centre, double-blind, placebo-controlled randomised trial. Babies who remained hypotensive despite treatment with volume expansion and dopamine (maximum dose 15 micrograms/kg/minute) were eligible. Babies who had been treated postnatally with glucocorticoids for longer than three days with a maximum equivalent dose of 0.5 mg/kg/day, and the last dose administered within seven days of study enrolment were excluded. Approximately 70% of babies had been exposed to antenatal steroids. Babies with a patent ductus arteriosus were not excluded. Hypotension was defined by identifying an 'individual minimum blood pressure' for each baby. This was determined by a complex algorithm including urine output, capillary filling time and target MAP ranges [MAP < 23 mmHg (babies with a birth weight < 750 g), MAP < 25 mmHg (babies with a birth weight 750 to 999 g),

MAP < 28 to 30 mmHg (babies with a birth weight 1000 to 2000 g), MAP < 35 mmHg (babies with a birth weight 2000 to 3000 g) and MAP < 40 mmHg (babies with a birth weight > 3000 g)]. Blood pressure was measured invasively using radial or umbilical arterial catheters. Infants received a single intravenous dose of dexamethasone 0.25 mg/kg or placebo (same volume of normal saline solution) concurrently with the start of the epinephrine infusion. The intervention compared, therefore, was epinephrine plus dexamethasone versus epinephrine plus placebo. Concurrent treatment with volume expansion was permitted.

Eight babies were randomised to receive dexamethasone and nine received placebo. The primary outcome was the duration of epinephrine therapy after administration of dexamethasone or placebo, and the end-point of the study was 12 hours after drug administration. Management of hypotension in general, and epinephrine therapy in particular, was standardised and protocol-based.

3. Ng 2006

This was a single centre trial of 48 infants assessing the efficacy of hydrocortisone in preterm infants with refractory hypotension in the first week of life. The design was a single centre double blinded, placebo controlled randomised trial. Infants less than 32 weeks gestation, with a birth weight of less than 1500 g with systemic hypotension refractory to volume expansion with isotonic saline up to 30ml/kg and dopamine infusion of >10 micrograms/kg/min within the first seven days of life were eligible. Infants with major lethal congenital or chromosomal anomalies, congenital heart defects, postnatal use of inhaled or systemic steroids prior to trial drug initiation, proven systemic infection, necrotising enterocolitis or having major surgery were excluded. The authors mention that most of the mothers received antenatal steroids (though the number has not been specified) and the cumulative dose of antenatal dexamethasone was similar in both groups. Hypotension was defined as MAP lower than the numerical value of the gestational age of the infant in completed weeks. Blood pressure was measured invasively through an indwelling arterial line. Hypotensive infants were treated initially with up to three fluid boluses of 10 ml/kg of isotonic saline. Hypotension unresponsive to volume expansion was treated with dopamine up to 20 microgram/kg/min, dobutamine up to 20 microgram/kg/min and epinephrine starting at 0.2 microgram/kg/min. The trial drug consisted of hydrocortisone given at a dose of 1mg/kg/dose every eight hours for five days.

Twenty four infants received hydrocortisone and 24 received placebo. The primary outcome was the weaning off vasopressor support within 72 hours of commencing the trial drug. Other outcomes studied included cumulative dose of volume expanders and vasopressors within the first 14 days of life and also serious short and medium term side effects of corticosteroids including hyperglycaemia, gastrointestinal complications and systemic infections.

4. Hochwald 2010

This was a small pilot trial published only in abstract form. Further data on trial methodology and outcomes were obtained through correspondence with the main author. Only published data was included in the final analysis. The design was a single centre double blinded, placebo controlled randomised trial. The

study reported on outcomes of 18 infants randomised to receive either hydrocortisone or placebo with hypotension non-responsive to one crystalloid bolus of 10ml/kg. Infants less than 28 weeks and below 1250 g in birthweight within the first 48 hours after birth were included. The exclusion criteria were major congenital abnormalities, congenital heart defects excluding PDA, proven systemic infection, necrotising enterocolitis, major surgery. Hypotension was defined as MAP lower than the numerical value of the gestational age of the infant in completed weeks. In infants with hypotension refractory to one fluid bolus, dopamine was commenced at 5 microgram/kg/min concurrently with the study drug going up to a maximum of 15 micrograms/kg/min. The study, therefore, compared the effects of hydrocortisone plus dopamine to placebo plus dopamine. The use of epinephrine starting at a dose of 0.2 micrograms/kg/min was permitted in refractory hypotension. Hydrocortisone was commenced at 2 mg/kg for the first dose followed by three six hourly doses of 1 mg/kg and a further four doses of 0.5 mg/kg giving a cumulative dose of 7 mg/kg in 48 hours.

Nine infants each received hydrocortisone and placebo. The primary outcome was the total cumulative dose of dopamine at 48 hours of study drug administration and by day seven of life. The secondary outcome was the total cumulative dose of epinephrine and total dose of fluids at 48 hours of study drug administration and by day seven of life. Other outcomes studied included the incidence of bronchopulmonary dysplasia, incidence of PDA and proportion of PDA requiring ligation, IVHs grade 3 and 4, incidence of PVL, incidence of NEC and proportion of NEC requiring surgery, NEC with perforation, positive blood cultures and survival to discharge.

Two further studies (Krediet 1998; Osiovich 2000) may prove to be eligible for inclusion, but as yet have only been published in abstract form and are awaiting further information and assessment prior to inclusion.

Excluded studies

Eighteen studies were considered for inclusion, but subsequently excluded for a variety of reasons. Details of these studies are given in the table 'Characteristics of excluded studies'.

Most of these studies represented case series or case-control studies of preterm babies who had received steroids for hypotension (Emery 1992; Fauser 1993; Helbock 1993; Visveshwara 1996; Tantivit 1999; Ng 2001; Seri 2001; Noori 2002; Juren 2003; Fernandez 2005; Noori 2006). Others were randomised controlled trials of inhaled or systemic steroids used as prophylaxis to prevent hypotension (Kopelman 1999; Vanhole 2002; Ng 2004; Efir 2005). Two studies studied the effects of steroids in term neonates with refractory hypotension (Tantivit 1999; Lespinasse 2001). One study compared the incidence of fungal infections in hypotensive preterm babies treated with hydrocortisone versus dexamethasone (Ramanathan 1996). The study by Bonsante 2007 was prophylactic trial of hydrocortisone compared to placebo on neonatal outcomes.

Risk of bias in included studies

Methodological quality was assessed using the standard method for conducting a systematic review described in the Cochrane Collaboration Handbook. Also see Table, Characteristics of Included Studies.

1. Minimisation of selection bias

In the study by [Bourchier 1997](#), allocation concealment was performed using a method of sealed envelopes containing a numerical code generated from a random number table. In the studies by [Ng 2006](#) and [Hochwald 2010](#) allocation concealment was performed similarly using sealed envelopes, but the codes being computer generated. In the study by [Gaissmaier 1999](#) also randomised infants, but the process of allocation concealment was not stated explicitly and was, therefore, classified as 'unclear'.

2. Minimisation of performance bias

[Bourchier 1997](#) did not attempt to mask caregivers with respect to the assigned treatment that an infant received. The two treatments were both administered intravenously, but dopamine was given as a continuous infusion and infants allocated to receive hydrocortisone were given intermittent bolus injections every four to six hours. The assignment group would, therefore, have been clear to the attending caregivers. The only way of effectively blinding caregivers would have been to give every study participant both a continuous infusion and an intermittent bolus injection, one of which would have been real and the other a placebo (a 'double-dummy' strategy).

In contrast, [Gaissmaier 1999](#) used a placebo control (isotonic saline solution) to mask caregivers to the group assignment. Ampoules of dexamethasone, or a corresponding volume of the placebo solution, were prepared by hospital pharmacy staff not directly involved in routine clinical management. [Ng 2006](#) and [Hochwald 2010](#) used a similar system of using isotonic saline as placebo. Both drugs were prepared in the pharmacy to similar volumes in syringes which were indistinguishable.

3. Minimisation of attrition bias

[Bourchier 1997](#) assessed all randomised infants for the primary outcome and secondary outcomes included in this review. [Gaissmaier 1999](#) randomised 20 infants, but three 'were later excluded from the analysis'. The reasons for exclusion were not stated. Two more infants were subsequently randomised, one of whom was again excluded because of hypertrophic obstructive cardiomyopathy (not a stated exclusion criterion). The authors report outcomes for 17 babies, leaving one further baby unaccounted for. Clearly, an intention-to-treat analysis was not performed in this study. [Ng 2006](#) assessed all 48 of the randomised infants for primary outcome. [Hochwald 2010](#) reported the findings on all 18 randomised infants for the primary outcome and other clinical outcomes.

4. Minimisation of detection bias

In none of the included studies, the method of masking for outcome assessors is not explicitly stated. Nevertheless, since the primary outcome was a short term outcome (that would have been assessed while the infant was still receiving the assigned treatment), one may assume that the outcome assessment was performed in a blinded manner in the [Gaissmaier 1999](#), [Hochwald 2010](#) and [Ng 2006](#) studies, but not in the study performed by [Bourchier 1997](#). Secondary outcomes would also have been assessed 'blind' in the [Gaissmaier 1999](#) study, since the assigned treatment was masked until study completion. It remains unclear whether any attempt was made to minimise detection bias in the assessment of secondary outcomes in the studies by [Bourchier 1997](#), [Hochwald 2010](#) and [Ng 2006](#).

Effects of interventions

Four studies were included in this review. Two trials ([Bourchier 1997](#); [Hochwald 2010](#)) related to the primary treatment of hypotension unresponsive to volume administration. One related to primary treatment of hypotension with hydrocortisone versus dopamine ([Bourchier 1997](#)) and the other ([Hochwald 2010](#)) assessed the efficacy of hydrocortisone compared to placebo. The other two trials ([Gaissmaier 1999](#); [Ng 2006](#)) assessed the efficacy of steroid treatment in hypotension refractory to treatment with inotropes. [Ng 2006](#) assessed the effect of hydrocortisone compared to placebo in refractory hypotension and the other trial ([Gaissmaier 1999](#)) investigated the effect of treatment of refractory hypotension with dexamethasone versus placebo.

See: Table of comparisons

PRIMARY TREATMENT OF HYPOTENSION

Comparison 1: Steroid versus placebo or nothing for the primary treatment of hypotension

In the trial by [Hochwald 2010](#) hydrocortisone with dopamine was compared to placebo with dopamine for the primary treatment of hypotension.

Mortality to discharge (Outcome 1.0)

In the single included trial ([Hochwald 2010](#)) there was no evidence of an effect of hydrocortisone on mortality compared to placebo (RR 0.14, 95% CI 0.01 to 2.42; RD -0.33, 95% CI 0.66 to -0.01).

IVH grades 3/4 (Outcome 1.2)

[Hochwald 2010](#) found no effect of hydrocortisone on severe intraventricular haemorrhage compared to placebo (RR 0.83, 95% CI 0.40 to 1.76; RD -0.11, 95% CI -0.56 to 0.34).

Periventricular leukomalacia (Outcome 1.3)

The single included trial ([Hochwald 2010](#)) found no significant difference in the incidence of periventricular leukomalacia between the groups treated with hydrocortisone or placebo (RR 2.00, 95% CI 0.22 to 18.33; RD 0.11, 95% CI -0.23 to 0.45).

Chronic lung disease in surviving infants (at 36 weeks post-menstrual age) (Outcome 1.4)

[Hochwald 2010](#) found no evidence of an effect of hydrocortisone on chronic lung disease (defined as oxygen dependency at 36 week post menstrual age) compared to placebo (RR 0.67, 95% CI 0.26 to 1.68; RD -0.22, 95% CI -0.72 to 0.28).

Necrotising enterocolitis (Outcome 1.5)

The single included trial ([Hochwald 2010](#)) showed no significant difference in the incidence of necrotising enterocolitis between the groups treated hydrocortisone or placebo (RR 0.14, 95% CI 0.01 to 2.42; RD -0.33, 95% CI -0.66 to -0.01).

Bacterial sepsis (Outcome 1.6)

[Hochwald 2010](#) found no significant increase in the risk of bacterial sepsis with the use of hydrocortisone compared to placebo in preterm infants for the treatment of primary hypotension (RR 0.33, 95% CI 0.09 to 1.23; RD -0.44, 95% CI -0.86 to -0.03).

Other outcomes

There are currently no data from included trials for the following outcomes:

Mortality (< 28 days), mortality (long term), cerebral palsy, developmental delay, sensorineural impairment, abnormal neurological examination, IVH all grades, chronic lung disease (at 28 days), gastrointestinal haemorrhage, gastrointestinal perforation, hyperglycaemia and fungal sepsis.

Comparison 2: Steroid versus other drug for the primary treatment of hypotension

[Bourchier 1997](#) and colleagues compared hydrocortisone to dopamine for the primary treatment of hypotensive preterm infants.

IVH all grades (Outcome 2.1)

[Bourchier 1997](#) reported data on IVH grades 2 to 4. There was no evidence of an effect of hydrocortisone on IVH versus dopamine (RR 1.51, 95% CI 0.42 to 5.48; RD 0.08, 95% CI -0.16 to 0.33).

Mortality to discharge (Outcome 2.2)

In the single included trial ([Bourchier 1997](#)), there was no evidence of an effect of hydrocortisone on mortality versus dopamine (RR 1.81, 95% CI 0.18 to 18.39; RD 0.04, 95% CI -0.12 to 0.20).

Retinopathy of prematurity in surviving infants (Outcome 2.3)

In the single included trial ([Bourchier 1997](#)), there was no evidence of an effect of hydrocortisone versus dopamine on retinopathy of prematurity (ROP) stages 2 to 4 (RR 1.26, 95% CI 0.33 to 4.88; RD 0.04, 95% CI -0.21 to 0.30).

Chronic lung disease in surviving infants (at 36 weeks post-menstrual age) (Outcome 2.4)

[Bourchier 1997](#) reported rates of chronic lung disease (CLD) in surviving infants defined as oxygen dependency at 36 weeks post-menstrual age. There was no evidence of an effect of hydrocortisone versus dopamine on the incidence of CLD (RR 2.37, 95% CI 0.52 to 10.7; RD 0.15, 95% CI -0.09 to 0.40).

Necrotising enterocolitis (Outcome 2.5)

There was no evidence of an effect of hydrocortisone versus dopamine on necrotising enterocolitis (NEC) (RR 3.62, 95% CI 0.44 to 29.6; RD 0.14, 95% CI -0.06 to 0.33) in the trial of [Bourchier 1997](#).

Hyperglycaemia (Outcome 2.6)

[Bourchier 1997](#) reported data on the incidence of hyperglycaemia with hydrocortisone, defined as the need for an insulin infusion. There was no evidence of an effect of hydrocortisone versus dopamine on hyperglycaemia (RR 1.27, 95% CI 0.48 to 3.33; RD 0.07, 95% CI -0.21 to 0.35).

Any sepsis (Outcome 2.7)

In the trial by [Bourchier 1997](#), there was no evidence of an effect of hydrocortisone versus dopamine on any sepsis (RR 0.60, 95% CI 0.20 to 1.82; RD -0.13, 95% CI -0.39 to 0.14).

Bacterial sepsis (Outcome 2.8)

There was no statistically significant effect on the incidence of bacterial sepsis (RR 0.60, 95% CI 0.20 to 1.82; RD -0.13, 95% CI -0.39 to 0.14) in the trial by [Bourchier 1997](#).

Fungal sepsis (Outcome 2.9)

[Bourchier 1997](#) reported no cases of fungal sepsis in infants treated with hydrocortisone or dopamine (RD 0, 95% CI -0.09 to 0.09).

Treatment failure (Outcome 2.10)

In the trial by [Bourchier 1997](#), treatment failure (persistent hypotension) was more common in hydrocortisone treated infants as compared to those who received dopamine, although this was of borderline statistical significance (RR 8.2, 95% CI 0.47 to 142.6; RD 0.19, 95% CI 0.01 to 0.37; NNT = 5.3, 95% CI 2.7,100).

Other outcomes

There are currently no data from included trials for the following outcomes:

Mortality (< 28 days), mortality (long term), cerebral palsy, developmental delay, sensorineural impairment, abnormal neurological examination, IVH grades 3/4, periventricular leukomalacia, chronic lung disease (at 28 days), gastrointestinal haemorrhage, gastrointestinal perforation, increase in mean blood pressure, increase in cardiac output or hypertrophic cardiomyopathy.

TREATMENT OF REFRACTORY HYPOTENSION

Steroid versus other drug (treatment of refractory hypotension)

There were no eligible trials to address this comparison.

Comparison 3: Steroid versus placebo or nothing

[Gaissmaier 1999](#) and colleagues compared dexamethasone to placebo in preterm infants with refractory hypotension. [Ng 2006](#) studied the effect of hydrocortisone compared to placebo in refractory hypotension.

Mortality to discharge (Outcome 3.1)

Both trials([Gaissmaier 1999](#); [Ng 2006](#)) reported mortality to discharge from hospital. There was no evidence of an effect of steroid versus placebo on mortality (RR 1.47 95% CI 0.53 to 4.09; RD 0.07, 95% CI -0.11 to 0.26).

Subgroup analysis-Mortality to discharge-Dexamethasone versus placebo (Outcome 3.1.1)

The single included trial ([Gaissmaier 1999](#)) reported mortality to discharge from hospital. There was no evidence of an effect of dexamethasone versus placebo on mortality (RR 1.69, 95% CI 0.37 to 7.67; RD 0.15, 95% CI -0.28 to 0.58).

Subgroup analysis-Mortality to discharge-Hydrocortisone versus placebo (Outcome 3.1.2)

[Ng 2006](#) reported the effect of hydrocortisone compared to placebo on mortality to discharge. There was no evidence of an effect of hydrocortisone on pre-discharge mortality compared to placebo (RR 1.33, 95% CI 0.33 to 5.33; RD 0.04, 95% CI -0.16 to 0.24).

IVH grades 3/4 (Outcome 3.2)

Both included trials([Gaissmaier 1999](#); [Ng 2006](#)) reported on intraventricular haemorrhage grade 3 or higher. There was no evidence of an effect of steroid versus placebo on severe IVH (RR 0.74, 95% CI 0.26 to 2.09; RD -0.05, 95% CI -0.24 to 0.13).

Subgroup analysis-IVH grades 3/4- Dexamethasone versus placebo (Outcome 3.2.1)

In the trial by [Gaissmaier 1999](#), there was no evidence of an effect of dexamethasone versus placebo on severe IVH (RR 1.13, 95% CI 0.20 to 6.24; RD 0.03, 95% CI -0.38 to 0.43).

Subgroup analysis-IVH grades 3/4- Hydrocortisone versus placebo (Outcome 3.2.2)

The single included trials (Ng 2006) showed there was no evidence of an effect of hydrocortisone on severe IVH compared to placebo (RR 0.60, 95% CI 0.16 to 2.23; RD -0.08, 95% CI -0.29 to 0.13).

IVH all grades (Outcome 3.3)

In the trial by Gaissmaier 1999, there was no evidence of an effect of dexamethasone versus placebo on all grades of IVH (RR 1.13, 95% CI 0.41 to 3.08; RD 0.06, 95% CI -0.42 to 0.53).

Subgroup analysis for this outcome was not possible as the other trial did not report on this outcome.

Periventricular leukomalacia (Outcome 3.4)

Meta-analysis of results from the two trials (Gaissmaier 1999; Ng 2006) found no evidence of an effect of steroids versus placebo on periventricular leukomalacia (RR 1.08, 95% CI 0.25 to 4.64; RD 0.01, 95% CI -0.13 to 0.14).

Subgroup analysis-Periventricular leukomalacia- Dexamethasone versus placebo (Outcome 3.4.1)

Gaissmaier 1999 found no evidence of an effect of dexamethasone versus placebo on periventricular leukomalacia (RR 1.13, 95% CI 0.20 to 6.24; RD 0.03, 95% CI -0.38 to 0.43).

Subgroup analysis-Periventricular leukomalacia- Hydrocortisone versus placebo (Outcome 3.4.2)

The study by Ng 2006 showed no evidence of an effect of hydrocortisone on periventricular leukomalacia compared to placebo (RR 1.00, 95% CI 0.07 to 15.08; RD 0.00, 95% CI -0.11 to 0.11).

Severe retinopathy of prematurity >Grade 2 (Outcome 3.5)

The single trial (Ng 2006) which reported this outcome showed no effect of hydrocortisone on the severe retinopathy (> grade 2) (RR 0.5, 95% CI 0.05 to 5.15; RD -0.04, 95% CI -0.18 to 0.09).

Chronic lung disease in surviving infants (at 36 weeks post-menstrual age) (Outcome 3.6)

The study by Ng 2006 showed no significant difference in the incidence of chronic lung disease amongst survivors in either the hydrocortisone or placebo treated infants (RR 1.13, 95% CI 0.52 to 2.42; RD -0.04, 95% CI -0.23 to 0.31).

Necrotising enterocolitis (Outcome 3.7)

Both the included trials (Gaissmaier 1999; Ng 2006) reported on the incidence of necrotising enterocolitis. Gaissmaier 1999 reported no cases of NEC in infants treated with dexamethasone or placebo. There was no evidence of increase in necrotising enterocolitis with the use of steroids (RR 0.67, 95% CI 0.12 to 3.64; RD -0.03, 95% CI -0.17 to 0.11).

Subgroup analysis-Necrotising enterocolitis- Dexamethasone versus placebo (Outcome 3.7.1)

Gaissmaier 1999 reported no cases of NEC in infants treated with dexamethasone or placebo (RD 0, 95% CI -0.20 to 0.20).

Subgroup analysis-Necrotising enterocolitis- Hydrocortisone versus placebo (Outcome 3.7.2)

The single trial assessing the efficacy of hydrocortisone (Ng 2006) showed no evidence of an effect of hydrocortisone on necrotising enterocolitis compared to placebo (RR 0.67, 95% CI 0.12 to 3.64; RD -0.04, 95% CI -0.21 to 0.13).

Gastric Bleeding (Outcome 3.8)

Ng 2006 showed no difference in the incidence of gastric bleeding between the hydrocortisone and placebo treated infants (RR 0.67, 95% CI 0.12 to 3.64; RD -0.04, 95% CI -0.21 to 0.13).

Gastrointestinal perforation (Outcome 3.9)

The single trial (Ng 2006) which reported this outcome showed no increase in gastro intestinal perforation with the use of hydrocortisone compared to placebo (RR 0.50, 95% CI 0.05 to 5.15; RD -0.04, 95% CI -0.18 to 0.09).

Bacterial sepsis (Outcome 3.10)

Both the included trials (Gaissmaier 1999; Ng 2006) reported on the incidence of bacterial infections. There was no evidence of an effect of steroids versus placebo on the incidence of bacterial sepsis (RR 1.09, 95% CI 0.29 to 4.10; RD 0.01, 95% CI -0.13 to 0.15).

Subgroup analysis-Bacterial Sepsis- Dexamethasone versus placebo (Outcome 3.6.1)

In Gaissmaier 1999, there was no evidence of an effect of dexamethasone versus placebo on the incidence of bacterial sepsis (RR 0.75, 95% CI 0.16 to 3.41; RD -0.08, 95% CI -0.51 to 0.35).

Subgroup analysis-Bacterial Sepsis- Hydrocortisone versus placebo (Outcome 3.6.2)

Ng 2006 showed there was no evidence of an effect of hydrocortisone on bacterial sepsis compared to placebo (RR 3.00, 95% CI 0.13 to 70.16; RD 0.04, 95% CI -0.07 to 0.15).

Treatment failure (Outcome 3.7)

Persistent need for inotropes despite treatment with steroids was reported in both the trials (Gaissmaier 1999; Ng 2006). The end points were different in the two trials with Gaissmaier 1999 reporting need for inotropes at 12 hours after treatment and Ng 2006 reporting the persistent need for inotropes at 72 hours. On meta-analysis of the results from both trials, the persistent need for inotropes was significantly less in the steroid treated infants compared to controls (RR 0.35, 95% CI 0.19 to 0.65; RD -0.47, 95% CI -0.68 to -0.26; NNT = 2.1, 95% CI 1.47, 3.8).

Subgroup analysis was not appropriate as there was only one study in each group.

Other outcomes

There are currently no data from included trials for the following outcomes:

Mortality (< 28 days), mortality (long term), cerebral palsy, developmental delay, sensorineural impairment, abnormal neurological examination, chronic lung disease (at 28 days), hyperglycaemia, any sepsis, fungal sepsis, increase in mean blood pressure, increase in cardiac output or hypertrophic cardiomyopathy.

DISCUSSION

We found four small studies that met our inclusion criteria for this review, with a further two studies that have only been published in abstract form to date, but may be eligible for inclusion in future updates. Two studies addressed the efficacy of corticosteroids as primary treatment in preterm hypotension. We were unable to perform a meta-analysis on the data on the efficacy of corticosteroids when used as primary treatment for hypotension as one compared hydrocortisone to dopamine whereas the other compared hydrocortisone to placebo. Two studies examined the

efficacy of corticosteroids in the treatment of refractory preterm hypotension. Two of the studies (Bourchier 1997; Gaissmaier 1999) contained deficiencies in methodological quality, but these were not considered to be significant enough to exclude them from inclusion in this review.

1. Corticosteroids for primary treatment of hypotension

Hydrocortisone may not be as effective as dopamine as primary treatment in preterm hypotension. There was no evidence that treatment with hydrocortisone was associated with an effect (either beneficial or detrimental) on other neonatal morbidities or on neonatal mortality in either of the included studies which looked at hydrocortisone as a primary treatment for preterm hypotension. It is important to emphasise that only one-third of babies in the study by Bourchier 1997 had been exposed to antenatal steroids and such data was not available in the study by Hochwald 2010. Since the use of antenatal steroids is associated with a decreased need for BP support in extremely low birth weight infants (perhaps through increasing neonatal circulating steroid concentrations), it could be argued that hydrocortisone therapy may be less effective in treating hypotension in preterm babies who have already been exposed to antenatal steroids. There was no evidence of a statistically significant effect of hydrocortisone

on potential adverse effects of steroid therapy such as infection or hyperglycaemia. The effect of hydrocortisone compared to dopamine with respect to long term neurodevelopmental outcome remains unknown.

2. Corticosteroids for treatment of refractory hypotension

Corticosteroid therapy for preterm infants with hypotension refractory to volume expansion and dopamine treatment, is associated with a statistically significant reduction in persisting hypotension (Figure 1). This benefit was demonstrated as a decrease in the continuing need for inotrope infusion in the studies by Gaissmaier 1999 and Ng 2006. The size of the observed effect (NNT, number needed to treat = 2) means that approximately two babies with refractory hypotension would have to be treated to enable cessation of inotrope therapy later in one baby. There was no evidence of a statistically significant beneficial effect of steroid therapy on short or medium term neonatal morbidity or mortality. Reassuringly, there was no evidence of a statistically significant effect of corticosteroids on potential adverse effects of steroid therapy such as infection, gastric bleeding or gastrointestinal perforation. However, the effect of corticosteroids especially dexamethasone on long term neurodevelopmental outcome remains unknown.

Figure 1. Forest plot of comparison: 3 Steroid versus placebo or nothing (treatment of refractory hypotension), outcome: 3.11 Treatment failure.

3. Limitations of the results of this review

The results of this review must be interpreted with caution. Only four studies were identified for inclusion enrolling a total of 123 babies. Given the small individual study sizes, there is substantial uncertainty (wide confidence intervals) around estimates of treatment effect. Therefore, even a relatively large, potentially clinically significant effect cannot reliably be excluded on the basis of these studies.

The studies used different definitions of hypotension, with only two recent studies using the same definition of blood pressure below the numerical value of gestation in weeks. The method of blood pressure measurement in the Bourchier 1997 study was not clear. All the studies concentrated only on relatively short-term effects such as successful treatment of hypotension, but the issue of long term safety and effectiveness was not addressed. None of the studies attempted to investigate changes in the wider range of haemodynamic parameters such as cardiac output, cardiac contractility or systemic vascular resistance and hence provided no information on the mechanism of action of steroids in increasing BP. Similarly, none of the studies provides information about any particular subgroups of patients who may benefit more from steroid therapy rather than continued 'conventional' treatment strategies.

AUTHORS' CONCLUSIONS

Implications for practice

1. There is insufficient evidence to support the routine use of hydrocortisone in the primary treatment of hypotension. Other corticosteroids have not been studied in randomised trials. There are insufficient data from randomised trials regarding the safety of steroids used for this indication.

2. Corticosteroids including dexamethasone and hydrocortisone may be effective in treating preterm infants with refractory hypotension receiving inotropes. Steroids seem to be safe in the short term when used for this indication. However given the lack of data on long term safety (and the concerns about the association between early post-natal dexamethasone use and subsequent cerebral palsy), neither dexamethasone nor hydrocortisone can be recommended for routine use in preterm hypotension.

Implications for research

A number of research questions need to be addressed including the following:

1. What is the relationship between preterm hypotension, cerebral blood flow, neurological injury in the neonatal period and long term neurodevelopmental outcome? What is the underlying pathophysiology? What other factors influence this relationship?
2. What is the relationship between adrenocortical function, cortisol levels and the development of hypotension in preterm infants? Are there particular groups of babies who may respond better to early steroid therapy?
3. Is there an identifiable threshold level of BP at which cardiovascular support (including steroid therapy) should be initiated?
4. Which agents (and at what doses and by which routes) are the most effective steroids for treating preterm hypotension? Are some drugs preferable to others in certain conditions (e.g. sepsis, lack of previous exposure to antenatal steroids etc.)?

5. What are the short and long term effects of steroid therapy? Do any long term benefits outweigh the potential long term risks of therapy?

6. Is prophylactic therapy with steroids safer and more effective than treatment of 'established' or refractory hypotension?

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bourchier 1997

Methods	Randomised Single centre trial Blinding of randomisation: yes Blinding of intervention: no Blinding of outcome assessment: unclear Complete follow-up: yes
Participants	Preterm hypotensive neonates Mean (SD) gestational age: 26.6 (2.1) in hydrocortisone-treated group versus 27.5 (1.6) in dopamine treated group. Mean (SD) birth weight: 923 (188) g in hydrocortisone-treated group versus 1043 (184) g in dopamine-treated group. Mean (SD) age: 11.4 (13.0) hours in hydrocortisone-treated group versus 15.1 (10.1) hours in dopamine-treated group. Treatment with antenatal steroids: 32.5% Pre-treatment with volume expansion: yes Pre-treatment with dopamine: no Concurrent treatment: volume expansion Major exclusions: major congenital abnormalities, shock requiring immediate inotropic support or treatment with blood products, clinically significant PDA, age > 7 days, birth weight > 1499 g.
Interventions	Hydrocortisone (N=21) versus dopamine (N=19) Route: IV Dose of hydrocortisone: 6 day course as follows: 2.5 mg/kg 4 hourly initially for 48 hours, 1.25 mg/kg 6 hourly for 48 hours, 0.625 mg/kg 6 hourly for 48 hours. Dose of dopamine: 5 micrograms/kg/minute initially to a maximum of 20 micrograms/kg/minute
Outcomes	Persistent hypotension despite treatment. Bronchopulmonary dysplasia (oxygen dependency at 36 weeks corrected gestational age) Intraventricular haemorrhage Sepsis
Notes	Definition of hypotension: BP < target defined according to birth weight. Method of blood pressure monitoring unclear. Study period 168 hours.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to treatment groups using random number table
Allocation concealment (selection bias)	Low risk	Sealed envelopes used for randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all randomised infants
Blinding of participants and personnel (performance bias)	High risk	Personnel not blinded to treatment

Bourchier 1997 (Continued)

All outcomes

Gaissmaier 1999

Methods	Randomised Single centre trial Blinding of randomisation: unclear Blinding of intervention: yes Blinding of outcome assessment: yes Complete follow-up: no
Participants	Preterm hypotensive neonates Gestational age: 25-36 weeks Birth weight: 450-2650g Age: 1-20 days Treatment with antenatal steroids: some Pre-treatment with volume expansion: yes Pre-treatment with dopamine: yes Concurrent treatment: epinephrine, volume expansion Major exclusions: congenital heart defect, previous administration of glucocorticoids < 7 days before study enrolment
Interventions	Dexamethasone (N=8) versus placebo (N=9) Route: IV Dose: 0.25mg/kg (dexamethasone) or equivalent volume of normal saline solution (placebo).
Outcomes	Duration of epinephrine infusion during first 12 hours post intervention.
Notes	Invasive BP monitoring Definition of hypotension: BP < individually determined minimum BP Rescue dose of dexamethasone given to babies who failed to respond to epinephrine and dexamethasone/placebo intervention. Three infants excluded post-randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not elaborated in study
Allocation concealment (selection bias)	Unclear risk	Method of randomisation and allocation not stated in study
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention to treat analysis not performed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate

Hochwald 2010

Methods	Randomised Single centre trial Blinding of randomisation: yes Blinding of intervention: yes Blinding of outcome assessment: unclear Complete follow-up: yes
Participants	Preterm Hypotensive infants Gestational age < 28 weeks Birth weight <1250g Age <48 hours Treatment with antenatal steroids: Most Pre-treatment with volume expansion: yes Pre-treatment with dopamine: Started concomitantly with study medication Concurrent treatment: volume expansion, dopamine,epinephrine Major exclusions:Clear evidence of hypovolaemia (blood loss),Chromosomal abnormalities,Hydrops fetalis, Major congenital anomalies,Cardiac lesions other than patent ductus arteriosus
Interventions	Hydrocortisone (N=9) versus placebo (N=9) Route: IV Dose of hydrocortisone: Initial dose of 2 mg/kg followed by 3 doses of 1 mg/kg 6hourly followed by 4 dose of 0.5mg/kg 6 hourly (Total 7mg/kg over 48 hours)
Outcomes	Primary Outcome : Total cumulative dose of dopamine at 48 hours of study drug administration and by day 7 of life Secondary Outcome : Total cumulative dose of epinephrine and total dose of fluids at 48 hours of study drug administration and by day 7 of life Others: Incidence of bronchopulmonary dysplasia, incidence of PDA and proportion of PDA requiring ligation,IVHs grade 3 and 4, incidence of PVL, incidence of NEC and proportion of NEC requiring surgery, NEC with perforation, positive blood cultures and survival to discharge
Notes	Invasive BP monitoring Definition of hypotension: BP < numerical value of gestational age in completed weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based random number generator used
Allocation concealment (selection bias)	Low risk	Sealed envelopes used for randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for all randomised infants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Personnel not blinded to treatment group

Ng 2006

Methods	Randomised Single centre trial Blinding of randomisation: yes Blinding of intervention: yes Blinding of outcome assessment: unclear Complete follow-up: yes
Participants	Preterm Hypotensive infants Gestational age <32 weeks Birth weight <1500g Age < 7 days Pre-treatment with volume expansion: yes Pre-treatment with dopamine: yes Concurrent treatment: volume expansion, dobutamine, epinephrine Major exclusions: major congenital abnormalities, congenital heart defects excluding PDA, Proven systemic infection, necrotising enterocolitis, major surgery
Interventions	Hydrocortisone (N=24) versus placebo (N=24) Route: IV Dose of hydrocortisone: 1mg/kg/ dose 8 hourly for 5 days
Outcomes	<u>Cardiovascular</u> Failure to wean off inotropes, Maximum, cumulative doses and duration of use of inotropes (dopamine, dobutamine and epinephrine), Use of volume expanders <u>Respiratory</u> Duration of ventilation, Duration of oxygen therapy, Maximum FiO ₂ , Maximum mean airway pressure, Chronic lung disease (oxygen at 36 weeks corrected gestation), Use of postnatal dexamethasone, Pulmonary haemorrhage, Pulmonary interstitial emphysema, Pneumothorax <u>Others</u> Highest serum glucose concentration, Glycosuria, Intraventricular haemorrhage grade 3 or higher, Periventricular leukomalacia, Necrotizing enterocolitis, Abnormal gastric aspirates, Gastrointestinal perforation, Age of achieving full enteral feeding, Episodes of culture proven sepsis, Retinopathy of prematurity stage III, Duration of hospitalisation, Mortality
Notes	Invasive BP monitoring Definition of hypotension: BP < numerical value of gestational age in completed weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation used in study
Allocation concealment (selection bias)	Low risk	Adequate-Sequentially numbered sealed envelopes used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all infants randomised available
Blinding of participants and personnel (performance bias)	Low risk	Personnel blinded to treatment group

Ng 2006 (Continued)
All outcomes

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bonsante 2007	Randomised trial of prophylactic hydrocortisone versus placebo.
Efird 2005	Randomised trial of prophylactic hydrocortisone versus placebo.
Emery 1992	Case study investigating the relationship between change in blood pressure after treatment with dexamethasone to postnatal age.
Fauser 1993	Retrospective case study of the effect on blood pressure of infants treated with dexamethasone.
Fernandez 2005	Retrospective cohort study evaluating correlation between low serum cortisol levels and response to hydrocortisone therapy.
Helbock 1993	Case study of the effects of glucocorticoid treatment on the blood pressure of six preterm neonates.
Juren 2003	Retrospective analysis of the response to early hydrocortisone in extremely low birth weight infants.
Kopelman 1999	Randomised trial of prophylactic dexamethasone versus placebo in preterm infants.
Lespinasse 2001	Retrospective case study of term infants treated with dexamethasone.
Ng 2001	Cases series of five infants with corticosteroid-responsive hypotension.
Ng 2004	Randomised trial of prophylactic inhaled steroid versus placebo.
Noori 2002	Case study of infants treated with dexamethasone for refractory hypotension.
Noori 2006	Observational study of hydrocortisone in refractory hypotension.
Ramanathan 1996	Study of hydrocortisone versus dexamethasone and incidence of candida infection.
Seri 2001	Retrospective review of the cardiovascular response to hydrocortisone of preterm infants with refractory hypotension.
Tantivit 1999	Trial observing baseline serum cortisol values and response to glucocorticoid therapy in hypotensive infants.
Vanhole 2002	Randomised placebo controlled trial of prophylactic hydrocortisone in preterm infants.
Visveshwara 1996	Case study of the effects on blood pressure of hydrocortisone.

DATA AND ANALYSES

Comparison 1. Steroid versus placebo for the primary treatment of hypotension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality to discharge	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.42]
2 IVH grade 3 or 4	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.40, 1.76]
3 Periventricular leukomalacia	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.22, 18.33]
4 Chronic lung disease in surviving infants (at 36 weeks post-menstrual age)	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.26, 1.68]
5 Necrotising enterocolitis	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.42]
6 Bacterial sepsis	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.09, 1.23]

Analysis 1.1. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 1 Mortality to discharge.

Analysis 1.2. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 2 IVH grade 3 or 4.

Analysis 1.3. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 3 Periventricular leukomalacia.

Analysis 1.4. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 4 Chronic lung disease in surviving infants (at 36 weeks post-menstrual age).

Analysis 1.5. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 5 Necrotising enterocolitis.

Analysis 1.6. Comparison 1 Steroid versus placebo for the primary treatment of hypotension, Outcome 6 Bacterial sepsis.

Comparison 2. Steroid versus other drug (primary treatment of hypotension)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IVH all grades	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.42, 5.48]
2 Mortality to discharge	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.18, 18.39]
3 Retinopathy of prematurity in surviving infants	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.33, 4.88]
4 Chronic lung disease in surviving infants (at 36 weeks post-menstrual age)	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.52, 10.70]
5 Necrotising enterocolitis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [0.44, 29.60]
6 Hyperglycaemia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.48, 3.33]
7 Any sepsis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.20, 1.82]
8 Bacterial sepsis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.20, 1.82]
9 Fungal sepsis	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Treatment failure	1	40	Risk Ratio (M-H, Fixed, 95% CI)	8.18 [0.47, 142.62]

Analysis 2.1. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 1 IVH all grades.

Analysis 2.2. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 2 Mortality to discharge.

Analysis 2.3. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 3 Retinopathy of prematurity in surviving infants.

Analysis 2.4. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 4 Chronic lung disease in surviving infants (at 36 weeks post-menstrual age).

Analysis 2.5. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 5 Necrotising enterocolitis.

Analysis 2.6. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 6 Hyperglycaemia.

Analysis 2.7. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 7 Any sepsis.

Analysis 2.8. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 8 Bacterial sepsis.

Analysis 2.9. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 9 Fungal sepsis.

Analysis 2.10. Comparison 2 Steroid versus other drug (primary treatment of hypotension), Outcome 10 Treatment failure.

Comparison 3. Steroid versus placebo or nothing (treatment of refractory hypotension)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality to discharge	2	65	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.53, 4.09]
1.1 Mortality to Discharge-Dexamethasone versus placebo	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.37, 7.67]
1.2 Mortality to Discharge-Hydrocortisone versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.33, 5.33]
2 IVH grade 3 or 4	2	65	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.26, 2.09]
2.1 IVH grade 3 or 4-Dexamethasone versus placebo	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.20, 6.24]
2.2 IVH grade 3 or 4-Hydrocortisone versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.16, 2.23]
3 IVH all grades	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.41, 3.08]
4 Periventricular leukomalacia	2	65	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.25, 4.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Periventricular leukomalacia-Dexamethasone versus placebo	1	17	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.20, 6.24]
4.2 Periventricular leukomalacia-Hydrocortisone versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.08]
5 Retinopathy of prematurity >Grade 2	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.15]
6 Chronic lung disease in surviving infants(36 weeks post menstrual age)	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.52, 2.42]
7 Necrotising enterocolitis	2	65	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.64]
7.1 Necrotising Enterocolitis-Dexamethasone versus placebo	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Necrotising Enterocolitis-Hydrocortisone versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.64]
8 Gastric bleeding	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.64]
9 Gastrointestinal perforation	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.15]
10 Bacterial sepsis	2	65	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.29, 4.10]
10.1 Bacterial Sepsis-Dexamethasone versus placebo	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.16, 3.41]
10.2 Bacterial Sepsis-Hydrocortisone versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.16]
11 Treatment failure	2	65	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.19, 0.65]

Analysis 3.1. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 1 Mortality to discharge.

Analysis 3.2. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 2 IVH grade 3 or 4.

Analysis 3.3. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 3 IVH all grades.

Analysis 3.4. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 4 Periventricular leukomalacia.

Analysis 3.5. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 5 Retinopathy of prematurity >Grade 2.

Analysis 3.6. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 6 Chronic lung disease in surviving infants(36 weeks post menstrual age).

Analysis 3.7. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 7 Necrotising enterocolitis.

Analysis 3.8. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 8 Gastric bleeding.

Analysis 3.9. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 9 Gastrointestinal perforation.

Analysis 3.10. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 10 Bacterial sepsis.

Analysis 3.11. Comparison 3 Steroid versus placebo or nothing (treatment of refractory hypotension), Outcome 11 Treatment failure.

WHAT'S NEW

Date	Event	Description
21 July 2011	New citation required but conclusions have not changed	<p>This update includes two new trials identified in the January 2011 search.</p> <p>The addition of these two trials did not change the conclusions of this review.</p>
21 July 2011	New search has been performed	<p>This is an update of the review "Corticosteroids for treating hypotension in preterm infants" published in the Cochrane Database of Systematic Reviews (Subhedar 2007).</p> <p>Updated search January 2011.</p>

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 1, 2007

Date	Event	Description
31 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

NVS was responsible for initiating the review, developing the original protocol and writing the original review and overseeing the project.

HI was responsible identifying the studies eligible for inclusion, extracting data from the included studies, contributed to the updated searches and updated the text based on new findings .

IS was jointly responsible for identifying eligible studies and extracting data from included studies.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool Women's Hospital NHS Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Nil

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Dexamethasone [therapeutic use]; Dopamine [therapeutic use]; Hydrocortisone [therapeutic use]; Hypotension [*drug therapy]; Infant, Premature; Infant, Premature, Diseases [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn