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Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions (Review)

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[Intervention Review]

Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions

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ABSTRACT

Background

Prostaglandin E1 (PGE1) is used to keep the ductus arteriosus patent and can be life-saving in neonates with ductal-dependent cardiac lesions. PGE1 is used to promote mixing of pulmonary and systemic blood flow or improve pulmonary or systemic circulations, prior to balloon atrial septostomy or surgery. PGE1 therapy may cause several short-term and long-term adverse effects. The efficacy and safety of PGE1 in neonates with ductal-dependent cardiac lesions has not been systematically reviewed.

Objectives

To determine the efficacy and safety of both short-term (< 120 hours) and long-term (≥120 hours) PGE1 therapy in maintaining patency of the ductus arteriosus and decreasing mortality in ductal-dependent cardiac lesions.

Search methods

We searched the literature in October 2017, using the search strategy recommended by Cochrane Neonatal. We searched electronic databases (CENTRAL (in the Cochrane Library), MEDLINE, CINAHL, Embase); abstracts of the Pediatric Academic Societies; websites for registered trials at www.clinicaltrials.gov and www.controlled-trials.com; and in the reference list of identified articles.

Selection criteria

Randomized or quasi-randomized trials using PGE1 at any dose or duration to maintain ductal patency in term or late preterm (≥ 34 weeks' gestation) infants with ductal-dependent cardiac lesions and which reported effectiveness and safety in the short term or long term.

Data collection and analysis

We followed the standard Cochrane methods for conducting a systematic review. Two review authors (SA and MP) independently assessed the titles and abstracts of studies identified by the search strategy to determine eligibility for inclusion. We obtained the full-text version if eligibility could not be done reliably by title and abstract. We resolved any differences by discussion. We designed electronic forms for trial inclusion/exclusion, data extraction, and for requesting additional published information from authors of the original reports.

Main results

Our search did not identify any completed or ongoing trials that met our inclusion criteria.

Authors' conclusions

There is insufficient evidence from randomized controlled trials to determine the safety and efficacy of PGE1 in neonates with ductal-dependent cardiac lesions. Evidence from observational trials have informed clinical practice on the use of PGE, which is now considered the standard of care for ductal-dependent cardiac lesions. It is unlikely that randomized controlled studies will be performed for this indication but comparative efficacy of newer formulations of PGE1, different doses of PGE1 and studies comparing PGE with PDA stents or other measures to keep the ductus open may be ethical and necessary.

PLAIN LANGUAGE SUMMARY

Prostaglandin E1 for keeping the duct open in heart conditions in the newborn

Review question:

Is keeping the ductus arteriosus open with prostaglandin E1 effective and safe in babies with heart conditions that need an open ductus arteriosus for survival?

Background

Ductus arteriosus is a blood vessel connection between the large blood vessel supplying blood to the lungs (pulmonary artery) and to the large blood vessel supplying blood to the body (aorta). Normally the ductus is open before birth and closes within the first day after birth. However, certain heart conditions where there is a block to the blood flow to the lungs or the body, or a condition where the blood vessels supplying the lungs and body are switched (transposition of great arteries), an open ductus is necessary for survival. Prostaglandin E1 (PGE1) is a substance produced by the ductus that keeps it open. External PGE1 is used to keep the ductus arteriosus open in neonates who have heart lesions that depend on an open ductus for survival. PGE1, though lifesaving, is not without risks. There are no systematic reviews to assess PGE1's effectiveness or safety.

Study characteristics:

We searched the literature for studies that used chance selection (randomization) that used PGE1 in neonates born at greater than 34 weeks of gestation to keep the ductus arteriosus open in newborn heart conditions and which reported on effectiveness and safety.

Key results:

We found no ongoing or completed randomized studies to include in this review. Currently there is no evidence from randomized trials on prostaglandin (PGE1) but information from non-randomized studies is available. Use of PGE1 in heart lesions, where the ductus arteriosus needs to stay open, is considered standard of care, and it would be perceived as unethical to do randomized studies.

Quality of evidence:

The quality of evidence could not be assessed as we found no randomized studies for inclusion in this review.

BACKGROUND

Description of the condition

In the developing fetus, the ductus arteriosus connects the pulmonary artery to the descending aorta, allowing most of the blood ejected from the right ventricle to bypass the nonfunctioning lungs and transfer to the aorta and then to the placenta for oxygenation. Endogenous prostaglandins, primarily prostaglandin E2 (PGE2)

and prostaglandin I2 (PGI2), are produced within the lumen of the ductus to maintain patency. At birth, an increase in arterial oxygen saturation and a decrease in endogenous prostaglandins promote closure of the ductus (Barst 1989; Roehl 1982). Infants with congenital heart disease (CHD) that are dependent on the patency of the ductus arteriosus for survival can be categorized into three groups. The first group is characterized by severe restriction of pulmonary blood flow (e.g. pulmonary atresia, tricuspid atresia or tetralogy of Fallot), where pulmonary circulation is dependent on the ductus arteriosus and postnatal constriction of the ductus causes severe hypoxemia, cyanosis and death (Momma 1980; Olley 1976). The second group includes conditions with severe restriction of systemic blood flow (e.g. aortic stenosis, coarctation of the aorta, interrupted aortic arch or left heart hypoplastic syndrome), where the systemic circulation is dependent on the ductus arteriosus and postnatal constriction of the ductus may cause systemic hypoperfusion, severe congestive heart failure and death (Heymann 1979). The third group includes cardiac anomalies (e.g. transposition of the great arteries; TGA), where adequate mixing of pulmonary and systemic blood flow is necessary for maintaining a circulation in series (Benson 1979; Lang 1979).

A neonate is said to have a ductal-dependent lesion when the pulmonary or systemic blood flow is dependent on the ductus arteriosus remaining patent. Ductal-dependent lesions include pulmonary atresia with intact ventricular septum, tetralogy of Fallot with pulmonary atresia, hypoplastic left heart syndrome, interrupted aortic arch and TGA with intact interventricular septum (IVS). In addition, variations of these defects, and others such as coarctation of the aorta, aortic stenosis, pulmonary stenosis, tricuspid atresia and truncus arteriosus, may also be considered ductus dependent. The availability of prenatal ultrasound scans including fetal echocardiography and postnatal CHD screening by pulse oximetry have identified neonates that are ductal-dependent and in whom prostaglandin E1 (PGE1) can be started to stabilize the infant's condition prior to surgery. In the absence of prenatal scans or postnatal pulse oximetry screening, neonates with ductal-dependent cardiac lesions may deteriorate after birth as the ductus constricts and becomes clinically symptomatic.

Description of the intervention

Alprostadil (PGE1) is a naturally occurring prostaglandin that was approved by the Food and Drug Administration (FDA) in 1981 for use in infants with CHD that required maintenance of ductal patency until palliative or corrective surgery could be performed (Roehl 1982). PGE1 is often used in neonates with prenatally diagnosed ductal-dependent cardiac disease in the immediate postnatal period (Marino 2001; Penny 2001; Shivananda 2010). Since 60% to 80% of PGE1 is metabolized on first pass through the lungs, it must be administered by continuous infusion. At a starting dose of 0.025 μg/kg/minute to 0.1 μg/kg/minute, the ductus usually reopens within 30 minutes to two hours of initiating PGE1, with the clinical response usually being instant if the duct is vital for the infant's hemodynamic status (Buck 1991). Since prostaglandin E has multiple physiologic effects, PGE1 therapy may be accompanied by several short-term and long-term adverse effects (Leoni 1984; Lewis 1981; Meckler 2009; Silove 1985; Teixeira 1984). Short-term adverse effects of PGE1 include apnea, peripheral vasodilation, fever and hypotension. In patients who were administered for more than five days, cortical hyperostosis (Estes 2007; Faye-Peterson 1996; Host 1988; Kalloghlian 1996; Momma 2005; Nadroo 2000; Persigehl 1984; Ringel 1982; Woo 1994), brown fat necrosis (Miller 2004; Raboi 1999), gastric outlet obstruction (Babyn 1995; Lacher 2007; Peled 1992; Perme 2013), and intimal mucosal damage (Calder 1984; Gittenberger-de Groot 1978) have been reported. In one study of infants with ductal-dependent pulmonary circulation, treatment with a lower initial dose of PGE1 of 0.02 μg/kg/minute and a maintenance dose of 0.01 μg/kg/minute was efficacious with a lower incidence of adverse effects (Huang 2013). Four PGE1 receptors (EP1, EP2, EP3 and EP4) have been identified and their specific distribution in tissues and organs has been reported in animal models (Kobayashi 2002). EP2 and EP4 receptor subtypes mediate PGE1-induced relaxation through a cyclic AMP-dependent mechanism, and EP1 and EP3 induce constriction (Smith 1995; Smith 1998; Smith 2001). EP3 has also been reported to mediate vasodilation of the ductus (Bouayad 2001). In human neonatal ductus arteriosus, the presence of EP3 and EP4 receptors has been reported (Leonhardt 2003). Theoretically, specific receptor subtype agonists may be more potent and have fewer adverse effects (Smith 1995; Smith 1998). In vivo dilation of rat neonatal ductus arteriosus by an EP4 receptor agonist has been studied (Momma 2005), and it is conceivable that agents that target specific PGE receptor subtypes may soon be available to modulate ductal tone selectively. Besides alprostadil, the use of other formulations of PGE1 such as lipo-PGE1 (Momma 1996; Takeda 2000), PGE1 α-cyclodextrin (Ramstad 2005), and an oral PGE1 derivative (Saji 1991) have been reported.

How the intervention might work

PGE1 is a potent dilator of the ductus arteriosus in human neonates (Reese 2010). Patency of the ductus allows for a right-to-left shunt where there is left ventricular (LV) outflow obstruction, thereby maintaining systemic blood flow; while it allows for a left-to-right shunt where there is diminished pulmonary blood flow, thereby maintaining pulmonary blood flow and allowing for mixing of blood between the right-sided and left-sided circulations when they are anatomically separated. In neonates with restriction of pulmonary blood flow, maintaining postnatal ductal patency with PGE1 can prevent severe hypoxia, cyanosis and death (Momma 1980; Olley 1976). In neonates with ductal-dependent systemic blood flow, PGE1 can relieve shock, anuria and congestive heart failure (Heymann 1979). In the case of anatomically

separated right and left heart circulations such as in TGA with intact ventricular septum, pulmonary blood flow elevates left atrial pressure and consequently increases left-to-right atrial shunting decreasing cyanosis (Benson 1979; Lang 1979). Long-term therapy with PGE1 has been used in infants awaiting surgery, in whom a longer period of growth and maturation is desired to reduce risk of surgery (Brodlie 2008; Teixeira 1984).

Why it is important to do this review

PGE1 is routinely used in infants with ductal-dependent cardiac lesions to improve circulation prior to balloon atrial septostomy or surgery (Barst 1989; Freed 1981; Graham 1978a; Graham 1978b; Heymann 1977; Lewis 1978; Neutze 1977; Olley 1976). However, the safety and the efficacy of PGE1 have not been systematically reviewed. Since PGE1 therapy may be lifesaving but not without risks, a systematic review of the safety and efficacy of PGE1 in ductal-dependent cardiac lesions is justified.

OBJECTIVES

To determine the efficacy and safety of both short-term (< 120 hours) and long-term (≥120 hours) PGE1 therapy in maintaining patency of the ductus arteriosus and decreasing mortality in ductal-dependent cardiac lesions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized, quasi-randomized, cluster-randomized or cross-over trials.

Types of participants

Term and late preterm infants (34 weeks' gestation or greater) with a ductal-dependent cardiac lesion.

Types of interventions

PGE1 in any formulation, dosage or duration used as a continuous infusion to maintain ductal patency.

Types of outcome measures

Primary outcomes

1. All-cause mortality at 28 days of life.
2. Mortality prior to cardiac surgery.
3. Improvement in the following cardiovascular and metabolic parameters expected due to ductal patency within four hours of therapy.

i) Increase in oxygen saturations (%) or partial pressure of oxygen dissolved in arterial blood (PaO_2 ; mmHg) (or both) by 10% (indicative of increased pulmonary blood flow in pulmonary obstructive lesions or increased mixing of blood from pulmonary and systemic circulations; e.g. TGA with intact ventricular septum).

ii) Decrease in the upper limb systolic blood pressure and increase in lower limb systolic blood pressure by 5 mmHg (improvement in systemic blood flow in systemic obstructive lesions).

iii) Improvement in metabolic acidosis defined arbitrarily by decrease in base deficit by 5 mEq/L or decrease in lactate by 2 mmol/L.

iv) Echocardiographic visualization of the patency of the ductus.

Secondary outcomes

1. Adverse effects

i) Short-term effects (within the first 120 hours of PGE1 therapy), as follows.

a) Hyperthermia (body temperature greater than 37.2 °C).

b) Jitteriness or seizures.

c) Apnea (cessation of breathing for 20 seconds or greater).

d) Diarrhea (more than eight stools per day or loose stools containing blood in the absence of radiologic evidence of necrotizing enterocolitis).

e) Arrhythmias.

f) Cutaneous vasodilation and flushing.

g) Hypotension (mean blood pressure less than 10th percentile for age).

ii) Long-term adverse effects (120 hours or greater of PGE1 therapy) evaluated any time during hospital stay or follow-up in the first six months of life.

a) Cortical hyperostosis of the long bones (measured by persistently elevated alkaline phosphatase and x-ray changes of extensive symmetrical periosteal reactions in long bones sometimes associated with clinical findings of limb edema).

b) Gastric outlet obstruction (measured by ultrasound findings of elongated and thickened pyloric musculature or marked antral mucosal hypertrophy).

c) Development of medial edema/hemorrhage, abnormal interruption of the internal elastic lamina and intimal tears (seen histologically after surgery or autopsy).

d) Radiographic visible calcifications corresponding to the anatomic distribution of brown adipose tissue especially along the great vessels of the neck, within the infraclavicular areas and axilla (suggestive of brown fat necrosis).

Comparisons

1. PGE1 by continuous intravenous infusion at any dose or duration or formulation versus placebo or no treatment.
2. Alprostadil versus other formulations of PGE1.
3. PGE1 and PDA stents.
4. PGE1 at different doses.

Search methods for identification of studies

We used the Cochrane Neonatal search strategy (neonatal.cochrane.org).

Electronic searches

We searched the following databases for relevant trials in any language in October 2017.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library (searched October 2, 2017).
2. Electronic journal reference databases: MEDLINE Ovid (1980 to 2 October 2017), PreMEDLINE, Embase Ovid (1980 to October 2, 2017) and CINAHL EBSCO (1982 to October 2, 2017).
3. Biologic abstracts in the database BIOSIS EBSCO; and conference abstracts from ProceedingsFirst (from 1992 to October 2, 2017).

Appendix 1 shows the search strategy for MEDLINE and PreMEDLINE. We adapted this strategy to suit CENTRAL, Embase and CINAHL.

Searching other resources

1. We searched the proceedings of Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Paediatric Research) from 1990 in the journal *Pediatric Research* and 'Abstracts2view' (2000 to 2017).
2. We searched for ongoing trials using ClinicalTrials.gov (www.clinicaltrials.gov), Current Controlled Trials (www.controlled-trials.com), the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp), and Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/TrialSearch.aspx).
3. We contacted authors who published in this field for possible unpublished studies.
4. We handsearched the reference lists of identified clinical trials and in the review authors' personal files.

Data collection and analysis

We followed Cochrane's standard methods for conducting a systematic review.

Selection of studies

Two review authors (AS and MP) independently assessed the titles and abstracts of studies identified by the search strategy for eligibility for inclusion in this review. We obtained the full-text version for assessment, if eligibility could not be assessed reliably by title and abstract. We resolved any differences by discussion. We obtained a full-text version of all eligible studies for qualitative assessment.

Data extraction and management

Two review authors (SA and MP) independently assessed the titles and abstracts of studies identified by the search strategy for eligibility for inclusion in this review. We obtained the full-text version for assessment if eligibility could not be assessed reliably by title and abstract. We resolved any differences by discussion. If we find eligible studies in the next version of this review, we will obtain a full-text version of all eligible studies for qualitative assessment.

Assessment of risk of bias in included studies

There are no included studies in this version of the review. For future updates of this review, two review authors (MP and SA) will independently assess the risk of bias for each included study using the criteria outlined by Cochrane Neonatal to assess the methodologic quality of the eligible studies (Higgins 2011).

1. Sequence generation: was the allocation sequence adequately generated? For each included study, we will describe the method used to generate the allocation sequence. We will assess the methods as:

i) low risk (any truly random process, e.g. random number table; computer random number generator);

ii) high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);

iii) unclear risk.

2. Allocation concealment: was allocation adequately concealed? For each included study, we will describe the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We will assess the methods as:

i) low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);

ii) high risk (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);

iii) unclear risk.

3. Blinding of participants, personnel and outcome assessors: was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment? For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or classes of outcome. We plan to categorize the methods as:

i) low risk, high risk or unclear risk for participants;

ii) low risk, high risk or unclear risk for personnel;

iii) low risk, high risk or unclear risk for outcome assessors.

4. Incomplete outcome data: were incomplete outcome data adequately addressed? For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We plan to assess the methods as:

i) low risk;

ii) high risk;

iii) unclear risk.

5. Selective outcome reporting: were reports of the study free of suggestion of selective outcome reporting? For each included study, we will describe how we examined the possibility of selective outcome reporting bias and what we found. We plan to assess the methods as:

i) low risk (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported);

ii) high risk (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; study did not include results of a key outcome that would have been expected to have been reported);

iii) unclear risk.

6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias? For each included study, we will describe any important concerns regarding other possible sources of bias. We plan to assess whether each study was free of other problems that could put it at risk of bias and categorize as:

i) low risk;

ii) high risk;

iii) unclear risk.

In cross-over trials, we will assess the following risks of bias as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Whether the cross-over design was suitable.
2. Whether there was a carry-over effect.
3. Whether only first-period data were available.
4. Incorrect analysis.
5. Comparability of results with those from parallel-group trials.

Measures of treatment effect

We will perform statistical analyses according to the recommendations of Cochrane Neonatal when eligible studies and data are available. We will analyze whether all infants randomized on 'an intention-to-treat basis' irrespective of whether they survived or not or received their allocated treatment completely. We will analyze treatment effects in the individual trials, using Cochrane's statistical analysis package, Review Manager 5 (Review Manager 2014).

We will report risk ratio (RR) and risk difference (RD) for dichotomous outcomes and mean difference (MD) for continuous outcomes with 95% confidence intervals (CI) of eligible trials. We will calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) with 95% CI if there is a statistically significant reduction or increase in RD.

In cross-over trials, if neither carry-over nor period effects are thought to be a problem, then we will use a paired t-test for continuous data from a two-period, two-intervention cross-over trial (Higgins 2011).

Unit of analysis issues

The unit of analysis is the participating infant in individually randomized trials, and the cluster (e.g. neonatal unit or subunit) for cluster-randomized trials.

Dealing with missing data

If we require clarifications or additional information, we will contact the authors of published studies. In the case of missing data, we will describe the number of participants with missing data in the 'Results' section and the 'Characteristics of included studies' table. We will only present the results for the available participants. We will discuss the implications of the missing data in the 'Discussion' of the review.

Assessment of heterogeneity

When data are available, we plan to estimate the treatment effects of individual trials and examine heterogeneity between trials by inspecting the forest plots and by using the Chi² test, which assesses whether observed differences in results are compatible with chance alone (Higgins 2011). A low P value (or a large Chi² statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). However, the Chi² statistic has low power when meta-analyzed studies have small sample size or are few in number. We will also quantify the impact of heterogeneity using the I² statistic (which incorporates the Chi² statistic). We will grade the degree of heterogeneity as none if the I² statistic is less than 25%, low if the I² statistic is between 25% and 49%, moderate if the I² statistic is between 50% and 74% or high if the I² statistic is greater than 75%. If we detect statistical heterogeneity, we will explore the possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) using post hoc subgroup analyses. We plan to use a fixed-effect model for meta-analysis.

Assessment of reporting biases

We will attempt to obtain study protocols of all included studies and compare outcomes reported in the protocols to those reported in the included studies. We will investigate reporting and publication bias by examining the degree of asymmetry of a funnel plot if at least 10 studies are included in the meta-analysis. Where we suspect reporting bias we will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by sensitivity analyses.

Data synthesis

We will use Review Manager 5 software for statistical analysis and intend to use a fixed-effect model for meta-analysis when eligible trials are identified (Review Manager 2014). We will perform statistical analyses according to the recommendations of Cochrane Neonatal. For cluster-randomized trials, if analyzed appropriately at the level of the cluster and if summary estimates are available, we will synthesize data using the generic inverse variance method. If summary estimates are unavailable or the trials were not analyzed at the cluster level, we will adjust the sample size by using the intracluster coefficient (ICC) and design effect (approximate analyses) (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses.

1. Gestational age:
   i) term (37 weeks or greater);
   ii) late preterm (34 to 36 weeks and six days).
2. Birth weight:
   i) 2500 grams or greater;
   ii) less than 2500 grams.
3. Participant subgroups based on the cardiac lesion:
   i) aortic obstructive lesions;
   ii) pulmonary obstructive lesions;
   iii) TGA or other parallel circulations that need mixing.
4. Duration of PGE1 administration:
   i) short-term (less than 120 hours);
   ii) long-term (120 hours or greater).
5. Timing of diagnosis of the cardiac disease:
   i) diagnosed prenatally or by pulse oximetry screening;
   ii) diagnosed after clinical manifestations.

Sensitivity analysis

We will explore methodologic heterogeneity using sensitivity analyses when eligible trials are identified and data are available.

RESULTS

Description of studies

Results of the search

We did not identify any studies that met our inclusion criteria. We excluded the studies that were not randomized controlled trials.

Included studies

We identified no eligible trials that met our inclusion criteria.

Excluded studies

Hallidie-Smith 1984

Hallidie-Smith and co-investigators tried to achieve an effective but safe regimen of PGE1 infusions in 52 sick neonates with major ductal-dependent cardiac defects. Effective clinical improvement was achieved at each dosage (0.005 μg/kg/minute and 0.1 μg/kg/minute), but the incidence of side effects were noted at a dosage of 0.005 μg/kg/minute to 0.01 μg/kg/minute. It was recommended that a low-dose regimen be started. This study was excluded because it was not a randomized control trial.

Ohara 1985

Ohara and co-investigators evaluated the effects of PGE1 infusion in 27 infants with ductal-dependent congenital heart disease. They concluded that PGE1 therapy is highly effective in stabilizing preoperative conditions of infants with ductal-dependent congenital heart disease. There were no fatal side effects during PGE1 infusion but it frequently caused apnea, the frequency of which

decreased with reducing the initial dose. This study was excluded because it was not a randomized controlled trial.

Ono 1980

Ono and co-investigators evaluated the effects of PGE1 in 21 infants with ductal-dependent congenital heart disease. Eleven infants responded favorably but developed complications like pyrexia, tachypnea, tachycardia, hypotension and apnea. In six patients to whom PGE1 was administered over three weeks, cortical hyperostosis was noted in two cases and hirsutism in one. It was concluded that PGE1 should be tried in infants who are critically ill because of decreased blood flow across the ductus, but complications of PGE1 administration are not rare. Therefore, PGE1 should be administered in the minimally effective dose as an adjunct to improve the perioperative state of babies. This study was excluded because it was not a randomized controlled trial.

Saxena 1998

Saxena and co-investigators evaluated the efficacy of PGE1 in 65 infants with ductal-dependent congenital heart disease. The drug was successful in 62 out of 65 cases with two failures and one discontinuation. Adverse effects included apnea, necrotizing enterocolitis, hyperpyrexia and jitteriness. Six patients died. Two were related to PGE1, one due to failure and another due to side effects. They concluded that PGE1 is an effective drug for keeping the ductus open in infants with ductal-dependent congenital heart disease. It can be used for neonates beyond the first week of life with efficacy. Apnea is a major side effect and close monitoring is essential. This study was excluded because it was not a randomized controlled trial.

Atik 1989

Atik and co-investigators evaluated 47 cases with ductal-dependent congenital heart disease in whom PGE1 infusion at a dose of 0.021 μg/kg/minute was used. Effective clinical improvement was achieved in pulmonary atresia, Ebstein anomaly, tricuspid atresia, hypoplastic left heart syndrome and tetralogy of Fallot. Side effects noted were apnea in 40.7%, hyperthermia and tachycardia in 19.1%, bradycardia and skin rash in 17%. They concluded that PGE1 has become an essential drug today in the management of neonatal congenital heart disease. This study was excluded because it was not a randomized controlled trial.

Babyn 1995

Babyn and associates investigated the long-term gastrointestinal effects of prostaglandin administration in neonates. Eight neonates had clinical, radiological and pathological evidence of gastric mucosal hyperplasia out of the study population of 74 neonates receiving PGE1. They concluded that long-term administration of PGE1 causes antral hyperplasia associated with feeding intolerance and gastric outlet obstruction. This study was excluded because it was not a randomized controlled trial.

Risk of bias in included studies

We did not identify any eligible studies for inclusion, and hence risk of bias could not be assessed.

Effects of interventions

We did not identify any eligible studies for inclusion.

DISCUSSION

Summary of main results

We did not identify any completed or ongoing studies that randomized neonates with ductal-dependent cardiac lesions to PGE1 or its analogues and which met our inclusion criteria.

Challenges in summarizing data on Prostaglandin E1 in neonates include variations in dose and duration of therapy. We identified studies and case reports which showed that PGE1 decreases mortality in the neonatal management of congenital heart disease (Atik 1989; Hallidie-Smith 1984; Ohara 1985; Ono 1980; Saxena 1998). All the above-mentioned studies were non-randomized, complicating unbiased assessment of clinical outcomes including adverse effects.

Adverse effects of prostaglandin E1 have been reported in some neonatal studies, and include apnea (Atik 1989; Ohara 1985; Ono 1980; Saxena 1998), tachypnea, tachycardia, hypotension (Ono 1980), hyperpyrexia (Atik 1989; Ono 1980; Saxena 1998), necrotizing enterocolitis (Saxena 1998), prolonged administration-caused cortical hyperostosis (Estes 2007; Kalloghlian 1996; Nadroo 2000; Ono 1980; Woo 1994), gastric outlet obstruction (Babyn 1995; Lacher 2007; Peled 1992; Perme 2013), and brown fat necrosis (Raboi 1999).

Very few studies have studied the dose-related side effects of PGE1 (Atik 1989; Hallidie-Smith 1984; Ohara 1985). These studies concluded that low-dose regimen is associated with fewer side effects. The safety of PGE1 needs to be assessed in prospective randomized controlled studies in neonates.

Overall completeness and applicability of evidence

We did not identify any randomized controlled trials inclusion. We found non-randomized studies that evaluated efficacy and safety of PGE1 in congenital heart disease. Observational studies including case-reports have reported improved survival after PGE1 administration in ductal-dependent congenital heart disease (Atik 1989; Hallidie-Smith 1984; Ohara 1985; Ono 1980; Saxena 1998). The presence of PGE receptors and relaxation of the ductus on stimulating a subset of these receptors lends biological plausibility to

the use of PGE1 in ductal-dependent cardiac lesions. Four PGE1 receptors (EP1, EP2, EP3 and EP4) have been identified and their specific distribution in tissues and organs has been reported in animal models (Kobayashi 2002). EP2 and EP4 receptor subtypes mediate PGE1-induced relaxation through a cyclic AMP-dependent mechanism, and EP1 and EP3 induce constriction (Smith 1995; Smith 1998; Smith 2001). EP3 has also been reported to mediate vasodilation of the ductus (Bouayad 2001). In vivo dilation of rat neonatal ductus arteriosus by an EP4 receptor agonist has been studied (Momma 2005). In human neonatal ductus arteriosus, the presence of EP3 and EP4 receptors has been reported (Leonhardt 2003); and the possibility of use of specific receptor subtype agonists is reported (Smith 1995; Smith 1998). Biological plausibility of ductal dilation with PGE1 and evidence from observational studies have informed clinical practice; and administration of PGE1 in ductal-dependent cardiac lesions is now the standard of care.

Quality of the evidence

We did not identify any trials so the issue of quality of evidence does not arise.

Potential biases in the review process

We strove to decrease biases in the review process. Both review authors performed the literature search using an inclusive search strategy and combined their results. Our search strategy did not identify any randomized controlled trials.

Agreements and disagreements with other studies or reviews

There are no other systematic reviews of the use of PGE1 in ductal-dependent cardiac lesions in neonates.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomized controlled trials to recommend or refute the use of prostaglandin E1 in the safe and effective treatment of ductal-dependent congenital heart disease. Importantly, there is limited information about the short- and long-term outcomes of neonates treated with prostaglandin E1. Evidence from non-randomized studies has informed clinical practice and currently prostaglandin E1 is considered the standard of care in neonates with ductal-dependent congenital cardiac disease.

Implications for research

Currently, since PGE1 is the standard of care, it would be considered unethical to randomize patients with ductal-dependent cardiac disease to prostaglandin infusion or not. However, comparative efficacy studies, comparing PGE with PDA stents or other measures to keep the ductus open may be ethical and necessary. Comparative efficacy of newer formulations of PGE1 are needed. Future non-randomized studies should address the efficacy, safety, timing of therapy, optimal dosing, impact of treatment on major morbidities in preterm infants such as necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and especially long-term neurodevelopmental, pulmonary outcomes and survival.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Atik 1989	Not a randomized controlled trial
Babyn 1995	Not a randomized controlled trial
Hallidie-Smith 1984	Not a randomized controlled trial
Ohara 1985	Not a randomized controlled trial
Ono 1980	Not a randomized controlled trial
Saxena 1998	Not a randomized controlled trial

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE and PreMEDLINE search strategy

#1 explode 'alprostadil' [all subheadings in MIME, MJME]
#2 PGE_1
#3 Prostaglandin E_1
#4 #1 OR #2 OR #3
#5 'congenital heart disease'
#6 'ductus-dependent'
#7 'ductal dependent'
#8 #5 OR #6 OR #7
#9 explode 'infant - newborn' [all subheadings in MIME, MJME]
#10 Neonat*
#11 Newborn*
#12 #9 or #10 or #11
#13 #4 AND #8 AND #12

PubMed search strategy

(((((alprostadil) OR Prostaglandin E1) OR PGE1)) AND ((ductus dependent) OR congenital heart disease)) AND (((newborn) OR infant-newborn[MeSH Terms]) OR neonat*)

CONTRIBUTIONS OF AUTHORS

SA and MP searched the literature, assessed inclusion eligibility and wrote the review.

SH and MP wrote the protocol.

CF, AC, MK and BS commented on the review and incorporated comments.

DECLARATIONS OF INTEREST

No conflicts of interest to declare for any author.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Alprostadil [adverse effects; *therapeutic use]; Ductus Arteriosus, Patent [*drug therapy]; Vasodilator Agents [adverse effects; *therapeutic use]

MeSH check words

Humans; Infant, Newborn