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REGULAR ARTICLE

The definition of a haemodynamic significant duct in randomized controlled trials: a systematic literature review

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ABSTRACT

Aim: A patent ductus arteriosus (PDA) is associated with morbidity in preterm infants. Treatment is prescribed for a haemodynamically significant duct (HSDA), but its definition varies. We systematically reviewed the clinical and ultrasound criteria used for the definition of an HSDA.

Methods: PubMed and the Cochrane library were searched for randomized trials evaluating ductal treatment. The included studies were explored, and we categorized clinical and ultrasound criteria used to define an HSDA.

Results: Sixty-seven trials were included in our review. Forty-two were placebo-controlled trials, and 25 were comparative trials. The diagnosis of the PDA was made by clinical examination, followed by ultrasound in most trials. Most trials used clinical and ultrasound criteria to define an HSDA, but there was a wide variety in criteria and cut-offs used. Of the clinical criteria, a murmur or hyperdynamic circulation was most used, and of the ultrasound criteria, the left-atrium-to-aorta ratio (LA/Ao ratio) was most used.

Conclusion: We found a wide variety in the definition of an HSDA. This finding implies that comparison of studies is difficult. International consensus should be reached on the definition of an HSDA, which will make future studies more comparable.

INTRODUCTION

A patent ductus arteriosus (PDA) with significant shunting is associated with several important morbidities in premature infants (1). Associated morbidity includes intraventricular haemorrhage (IVH), low systemic blood flow, low blood pressure, necrotizing enterocolitis, increased and prolonged respiratory support and chronic lung disease. The underlying pathophysiology is often described as a steal of blood away from the systemic circulation and, if significant shunting persists, cardiac and pulmonary volume (2).

Treatment is commonly prescribed for a haemodynamically significant ductus arteriosus (HSDA). Most short- and long-term outcomes have not been shown to be affected by treatment. All Cochrane systematic reviews evaluating prevention of or treatment for a PDA with medical or surgical treatment showed a significant reduction in ductal patency with all treatment approaches (3–9). Prophylactic indomethacin, given in the first 24 h of life, was the only treatment approach that could reduce severe IVH, but without the expected improvement in neurodevelopment (4). Surgical ligation as treatment option was often associated with harm (7,10). Benitz proposed that it is time to accept the null hypothesis and questions the necessity to treat the PDA (11). He proposes a trial that compares PDA closure versus treatment not primarily intended to achieve closure in a high-risk population. Although we feel this trial is most needed, we question the available evidence on how the actual diagnosis of a PDA was made and whether shunt severity was taken into account. So, the aim of this study is to systematically review which clinical and/or ultrasound parameters were used to diagnose a PDA and classify the PDA as haemodynamically significant in randomized controlled trials evaluating ductal treatment.

METHODS

We searched PubMed and the Cochrane library to find all randomized controlled trials evaluating PDA treatment using the Mesh terms ‘ductus arteriosus, patent’ and

Key notes

- A ductus arteriosus is commonly treated when it is deemed haemodynamically significant.
- We categorized randomized trials evaluating ductal treatment in which clinical and ultrasound criteria were used to define a haemodynamically significant ductus arteriosus (HSDA).
- We found a wide variety in the definition of an HSDA, which implies that comparison of studies is difficult.

'randomised controlled trial'. Selection of papers for possible inclusion in this systematic review was performed independently by both authors, and full-text articles of selected papers were retrieved and evaluated for inclusion. References of selected papers were also evaluated for inclusion. A study was included if it was a randomized trail evaluating ductal treatment and reported on ductal closure. Abstracts of studies were not included as they usually do not contain sufficient detailed information. Studies of ductal treatment outside the neonatal period and papers in languages we could not translate were excluded as well.

The included studies were explored for inclusion criteria of patients, study design, timing of treatment, how the diagnosis of a PDA was made and the clinical and/or ultrasound criteria used to define an HSDA. Many different descriptions of a persisting PDA have been used, being described as symptomatic, clinically significant, and haemodynamically important. In this study, we use the term HSDA to encompass all of these, and it will be used to describe the moment when the investigator decides to randomize or start treatment after 24 h of life.

The inclusion criteria were categorized into studies that only included preterm infants <30 weeks of gestation and/or <1500 g and studies that also included more mature and bigger infants. Study design was categorized as a placebo-controlled trial or a comparative trial comparing different treatments or drugs, drug dose, drug duration, drug route of administration or timing of treatment. The studies were categorized as early treatment if randomization or treatment was started within 24 h of life and as later treatment if randomization or treatment was started after 24 h of life. Early treatment studies often did not explore whether a PDA was present at the start of the trial, so we collected data on the diagnosis and definition of an HSDA when re-treatment for a PDA was started. For later treatment studies, the entry criteria for the trial were used. This approach means we are reviewing the PDA diagnosis and the definition of an HSDA after the first 24 h of life only.

The clinical criteria used for the definition of an HSDA were categorized as follows: (i) respiratory signs, including increased respiratory support, unable to wean respiratory support or oxygen need; (ii) physical signs, including a murmur, hyperdynamic precordium or bounding pulses; (iii) blood pressure problems, including decreased mean or diastolic pressure or increased pulse pressure, and/or (iv) signs of congestive heart failure, including cardiomegaly, hepatomegaly or pulmonary congestion. Ultrasound criteria used for the definition of an HSDA were also categorized into four categories: (i) left heart dimensions, including the left-atrium-to-aorta ratio (LA/Ao ratio) and left ventricular dimensions, (ii) left-to-right shunting, including the presence of a colour jet in the mean pulmonary artery, bubble contrast studies, aortograms and studies that mentioned 'any left-to-right shunting' but did not specify further, (iii) Doppler parameters, including ductal jet size, detailed descriptions of ductal turbulence in the mean pulmonary artery or reverse flow in any vessel in the body, and/or (iv) ductal diameter. For both the clinical and ultrasound criteria, more than one category could be assigned to each study.

Meta-analysis of studies using inclusion criteria reflecting a population less likely to show spontaneous closure and criteria of significant ductal shunt severity was attempted. Papers that studied infants ≤30 weeks and/or ≤1500 g only and used a ductal diameter >1.5 mm and/or reverse flow in any vessel as ultrasound criteria for treatment were eligible. Data on short-term clinical outcomes were extracted independently by both reviewers and entered into Review Manager software for meta-analysis (RevMan version 5; Cochrane.org.). All categorical outcomes are expressed as odds ratio and 95% confidence intervals.

RESULTS

Our search in PubMed in August 2010 revealed 251 hits on 'ductus arteriosus, patent' and 'randomised controlled trial'. After excluding papers not describing our topic (179), a letter to the editor and three trials in a language we could not translate, 58 trials were evaluated for inclusion in our systematic review. The Cochrane library revealed 10 systematic reviews evaluating ductal treatment and provided 10 extra trials for inclusion not found with PubMed. Cross-referencing found one extra trial for inclusion. After evaluating the full-text papers, we excluded one paper as it did not report on ductal closure and one paper providing insufficient detailed information, leaving 67 papers to be included in this systematic review (list of references of included studies available from the authors).

There were 42 placebo-controlled trials and 25 comparative trials. Twenty-eight trials were early treatment trials and 39 later treatment trials. Thirty-six trials included only infants <30 weeks of gestation and/or <1500 g, and in 27 trials, respiratory support was an important inclusion criterion for the study.

How the diagnosis of a PDA was established and which criteria were used for the definition of an HSDA are presented in Table 1. Twenty-five per cent of the included studies did not mention how the diagnosis of a PDA was established. Most studies would diagnose a PDA using clinical criteria first, followed by an ultrasound to confirm its presence. The definition of an HSDA was made up of clinical and ultrasound criteria in most studies.

The clinical and ultrasound criteria as categorized for the definition of an HSDA are presented in Table 2. Most studies included physical signs in the definition of an HSDA, but only one-third of the studies included respiratory signs. Signs of congestive heart failure were often quoted, but very few studies provided a definition for this clinical entity. The ultrasound criteria most commonly included the LA/Ao ratio, with a median cut-off of more than 1.30. The range of cut-off for the LA/Ao ratio varied between 1.15 and 1.70. Of the Doppler parameters used, reverse flow in various vessels in the body was always classified as severe shunting in the studies. The median cut-off to consider a PDA as significant using ductal diameter was over 1.5 mm, with a range between 1.5 and 2.0 mm. Only

Table 1 The establishment of the diagnosis of a PDA and the criteria used for the definition of an HSDA in 67 randomised trials evaluating ductal treatment

How was the PDA diagnosis established	Studies (%)	Criteria used for the definition of an HSDA	Studies (%)
Not mentioned	17 (25)	Not mentioned	3 (4)
Clinical only	7 (10)	Clinical only	7 (10)
Clinical, then ultrasound	41 (62)	Clinical and ultrasound	44 (66)
Ultrasound only	2 (3)	Ultrasound only	13 (20)

HSDA = haemodynamically significant duct; PDA = patent ductus arteriosus.

Table 2 The clinical and ultrasound parameters used in the definition of an HSDA

Clinical criteria used for the definition of an HSDA	Studies	Ultrasound criteria used for the definition of an HSDA	Studies
Respiratory signs	22	Left heart dimensions	34
Physical signs	36	Left to right shunting	18
Blood pressure	7	Doppler parameters	21
Congestive heart failure	26	Ductal diameter	8

HSDA = haemodynamically significant duct.

two of the eight studies using ductal diameter gave a detailed description or reference on how and where the ductal diameter was measured.

We re-analysed placebo-controlled studies using inclusion criteria reflecting a population less likely to show spontaneous closure (≤30 weeks and/or ≤1500 g) and significant ductal shunt severity when treated (ductal diameter >1.5 mm and/or reverse flow in any vessel). We found six trials that matched our inclusion criteria (12–17). There was a significant reduction in ductal patency, but no reduction in mortality and important clinical outcomes (Table 3).

Table 3 Results of meta-analysis of six placebo-controlled trials including only patients ≤30 weeks and/or ≤1500 g with an HSDA defined as a ductal diameter >1.5 mm and/or a reverse flow in any vessel[12–17]

	Trials/Patients	Odds ratio	95% Confidence interval
Ductal patency	6/933	0.31	0.23–0.42
IVH grade 3 and 4	5/893	0.91	0.60–1.34
NEC (>Bell's 2)	5/894	1.06	0.60–1.86
ROP (>Grade 2)	3/250	1.04	0.44–2.46
Oxygen need at 36 weeks	6/940	1.06	0.80–1.42
Mortality	6/933	0.86	0.61–1.23

HSDA = haemodynamically significant duct; IVH = intraventricular haemorrhage.

DISCUSSION

We found a wide variety in inclusion criteria of the studies, in the establishment of the PDA diagnosis and how the PDA was categorized as an HSDA. This finding suggests it is likely that many studies randomized PDAs with significant differences in ductal shunting, and therefore, treatment outcomes do not necessarily reflect the effect of a major reduction in ductal shunting. When performing meta-analysis, it would be optimal if all included studies used a uniform definition of the diagnosis of the problem at hand. This was not the case for systematic reviews evaluating ductal treatment, and one could question the validity of the results of these systematic reviews. When we re-analysed all the placebo-controlled trials on diagnostic criteria reflecting significant ductal shunting, we did not find a different treatment effect compared with the results of the Cochrane systematic reviews.

The available systematic reviews do provide information for hypothesis and future research on ductal treatment. Selection of patients for inclusion and developing an international consensus for the definition of an HSDA are important considerations for future studies.

It seems that preterm infants who are unnecessarily exposed to treatment (i.e. have the tendency to close their duct spontaneously) probably do not benefit from treatment or may even suffer adverse effect. Early targeted treatment at 3–12 h after birth, a time point when steal from the systemic circulation can occur, will give the opportunity to select patients based on ultrasound parameters of non-constriction. The Australian DETECT study is currently investigating this strategy with primary outcome combined death and abnormal cranial ultrasound (18).

A Cochrane systematic review suggests that asymptomatic treatment after 24 h of life does not improve major clinical outcomes, and other evidence shows that early treatment does not provide better clinical outcomes if compared with later treatment (3,12,19,20). This effect is most likely due to the high rate of spontaneous closure during this period, and it seems questionable whether new trials randomizing infants without significant clinical signs at this point in time could prove beneficial.

A symptomatic PDA after the transitional period has not been extensively studied in placebo-controlled trails. Treatment could be targeted on haemodynamically significant ducts causing important clinical problems on repeated evaluations, but an international consensus on the definition of an HSDA is lacking. We can provide suggestions of what we would consider an HSDA after the transitional period, based on little empirical evidence. We suggest evaluating a ductus arteriosus in a population most at risk (e.g. gestational age <30 weeks and/or birth weight <1500 g) in infants with clinical signs and always use ultrasound for confirmation of ductal presence and haemodynamic classification. For clinical signs, we would suggest respiratory signs (increased respiratory support, unable to wean respiratory support) or severe clinical signs such as hypotension as early presenting sign and/or congestive heart failure later during the clinical course. These are the signs we would like to see improved in our patients. The commonly mentioned physical signs such as a murmur and/or a hyperdynamic circulation should probably not be used to initiate treatment.

Of the ultrasound parameters, information about shunt size and cardiac (de)compensation is needed. Flow through a vessel is dependent on the diameter and the

pressure gradient. The diameter will contribute most to the amount of flow over a vessel and should be incorporated into the definition of an HSDA. Many investigators have studied ductal diameter using the high left parasternal view to visualize the duct in its whole length and look for the site of maximal constriction during end-systole with colour images (21,22). This methodology is not universal, and ductal diameter can vary significantly from the pulmonary end to the aortic end, so local standardization of diameter measurements and reporting will benefit future comparisons. Reverse flow in the descending aorta at the level of the diaphragm and a pulsatile shunt pattern are associated with ductal diameter and could be used in conjunction to validate the diameter measurements (22–24). Evaluating cardiac (de)compensation with ultrasound is more difficult but should include measures of left ventricular volume and pressure loading. The LA/Ao ratio is still a valid measurement of left ventricular volume loading, but the cut-off value that represents significant volume overload is often higher than the median value found in this systematic review (25). For volume load, we use the measurements and values as proposed by McNamara et al. (26) and also find that a large mitral regurgitant jet is associated with clinical volume overload. Ductal constriction usually precedes the ultrasound signs of volume overload, so we would not recommend using volume load parameters alone. As there seems to be no benefit from immediate treatment for a PDA based on the current available evidence, it would be reasonable to initiate treatment only if the clinical and ultrasound criteria of haemodynamic significance are found on two or more evaluations. For example, not all respiratory signs are caused by ductal patency, and some might benefit more from optimizing respiratory support first. Time often provides clinical improvement and ductal constriction or closure (27).

In conclusion, we found a wide variety in the definition of an HSDA in randomized trials evaluating ductal treatment. This finding implies that comparison of the studies performed thus far is difficult. International consensus should be reached on the definition of an HSDA, which will make future studies more comparable.

CONFLICTS OF INTERESTS

None.

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