**The uPDA trial (Pilot Trial)**

**The ‘ultimate’ PDA trial; Early pharmacological treatment with supportive care versus supportive care alone in preterm infants with a patent ductus arteriosus**

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**Initial recruitment sites**

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**Synopsis**

Preterm birth continues to be a major health problem throughout the world. Very preterm babies have to adapt to their new extra uterine environment to be able to survive, often with increased risks of abnormal neurodevelopmental outcomes in later life.

A patent ductus arteriosus (PDA) is a frequent cardiovascular complication in this patient group, and many would receive treatment with either medication or surgical closure. However, meta-analysis of trials showed no improvement in clinical outcomes, even though PDA was reduced. It is possible that the treatment received is causing more harm than benefit or treatment is being directed at the wrong patient subgroups.

A definitive trial, comparing current standard treatment (pharmacological treatment with supportive care) versus supportive care alone, is necessary to resolve doubts regarding the quality or conduct of prior studies. We hypothesise that there will be comparable outcomes between the 2 approaches, and that this data will support the start of a larger trial using neonatal and cardiology collaboration networks. The proposed study design where no open label pharmacological treatment is allowed will be able to describe the natural course of a PDA in preterm infants in the current era of perinatal care. It will allow for detailed prospective study of the PDA using conventional and novel echocardiography techniques to address the issue of which patient subgroups may benefit from treatment.

**Background**

The ductus arteriosus (DA) is a vascular structure joining the aorta and pulmonary artery that normally closes soon after birth. A patent ductus arteriosus (PDA) results from failure of the ductus arteriosus to close or from reopening after functional closure. A PDA is a common problem in very preterm infants. Over half of preterm infants less than 29 week gestation develop clinical signs associated with a PDA or a PDA is found on routine ultrasound in asymptomatic infants.1 Most of them will receive treatment, as early studies have shown associations between a PDA and major morbidity in very preterm infants.

The current treatment of a PDA is aimed at closure of the PDA with the use of non-steroidal anti-inflammatory drugs (NSAIDs), commonly indomethacin or ibuprofen. If medical management fails and the DA remains symptomatic then surgical ligation is the second line of treatment. Trials using NSAIDs and trials designed to close the PDA have provided insight into the contribution of the DA to morbidity as well as efficacy of therapy. Prophylactic indomethacin given early after birth has been trialed with success to help reduce the incidence of severe intraventricular hemorrhage in preterm infants. Reduced ductal patency was seen as additional effect, but these early benefits did not alter the incidence of later neonatal morbidity, including chronic lung disease and neuro-developmental outcomes.2 Trials where NSAIDs were given from 24 hours after birth to symptomatic or asymtopmatic infants all show reduced ductal patency without changing neonatal mortality or morbidities.3

It seems that the current treatment approach is not reducing morbidities commonly attributed to a PDA. This poses the possibility that the treatment is causing more harm than benefit, or treatment is being directed at the wrong patient subgroups. Indomethacin is a potent unselective vasoconstrictor. Adverse effects include a transient decrease in cerebral, cardiac, mesenteric and renal perfusion, and increased risk of gastrointestinal perforation, necrotising enterocolitisand renal impairment.4 Ibuprofen appears to have less adverse effects on organ blood flow, but may increase the risk of chronic lung disease.3 There is also a body of evidence showing increased morbidity in infants who underwent surgical ligation of the PDA after failed NSAID treatement.5,6

In light of the reports, some authors have advocated avoiding NSAIDs and surgical ligation.7,8 Potential adverse effects of such a permissive approach is prolonged exposure of the pulmonary artery system to high-pressure and increased flow that could lead to heart failure or irreversible pulmonary vascular disease.9 Uncertainty remains about how long a newborn can be exposed to such physiology before these adverse changes take place. The natural course of a PDA in infants has never been fully established due to the high rate of open label medical treatment or surgical ligation of all PDA’s since its first report in 1939.Term infants who develop signs of a PDA during infancy would commonly receive treatment at 6 to18 months. In contrast, most preterm infants with a PDA would receive treatment within the first week, and surgical ligation is commonly performed before 5 weeks of life.

Our group recently presented unique data on the development of heart failure in preterm infants with a PDA.10 A PDA primarily increases cardiac volume and size with preserved systolic function and altered atrial function. Clinical signs of heart failure were common in this cohort, but the clinical and cardiac changes associated with heart failure were not progressive with prolonged exposure to a PDA and generally resided after 5 to 6 weeks. In addition, most PDA’s constrict or close before discharge from the neonatal intensive care unit.8,11

A new well designed trial is needed to answer some of the current clinical questions regarding PDA treatment in preterm infants. We surveyed clinicians’ attitude on the requirements for a new PDA trial design that would change their practice if completed. Consensus was found for most items that have to be considered in any new PDA trial, and are incorporated in the current proposed trial.12

**Aim:**

The aim of this study is to trial in preterm infants if PDA management utilising supportive care without NSAIDs is equally effective compared to standard PDA treatment with supportive care and NSAIDs. The primary outcome of this pilot study is death and/or chronic lung disease (oxygen dependency at 36 weeks corrected gestational age). Secondary outcomes include neonatal morbidities associated with early hemodynamics changes (pulmonary haemorrhage, IVH, NEC) and neurodevelopmental impairment.

**Methods:**

*Subjects*

Preterm infants less than 29 weeks (23+0 to 28+6) gestation will be eligible

*Inclusion*

Infants can be included if at a cardiac ultrasound before 72 hours after birth a PDA > 1.5 mm with predominantly (>67%) left-to-right shunt is found

*Exclusion*

Exclusion criteria are a significant active haemorrhage (pulmonary, IVH grade 3 or 4, other) at randomization, major congenital heart disease, significant other congenital abnormalities, and absolute contraindications for NSAIDs.

*Randomisation*

After signed informed consent, infants will be randomized to standard treatment (3 doses of intravenous NSAID) or placebo. A randomisation number list with study IDs will be generated by the each hospital pharmacy department which will be stored in numbered sealed envelopes. The research nurse/ or nurse unit manager/team leader will take the next available envelope. Inside will be the study ID number and treatment allocation. Study drug administration is according to local drug protocol (See local administration guide).

As per standard guideline, a course of study drug (of the allocated randomisation arm) can be repeated if the cardiac ultrasound findings 24-48 hours after the first course is completed remain unchanged. Supportive care management in both groups is directed at discretion of the clinician.

*NSAID*

This is a pragmatic study evaluating NSAID therapy with supportive care versus supportive care alone in the management of PDA. Both commonly used NSAID preparations will be eligible and can be used according to current local guidelines. Indomethacin is known to be more effective in very early treatment (<24h). Ibuprofen has a better side effect profile when used in early treatment (24-72h). The standard recommended dose and interval are

Indomethacin iv 0.2-0.1-0.1 mg/kg with 24 hour intervals

Ibuprofen iv 10-5-5 mg/kg with 24 hour intervals

*Supportive care*

Supportive care includes optimizing airway pressure, careful fluid management with or without the use of diuretics. No directive guideline is provided with this study, as none of the suggested interventions have been rigorously tested. The following recommendations for management are provided:

Positive end expiratory pressure (PEEP)

PEEP has the potential of reducing shunt volume of a PDA. The optimal pressure is not known, but reported as at least 4.5 and no greater than 8 cmH2O.

Fluid management

No consensus is available on fluid restriction in PDA management. The available evidence suggests a 10-20% reduction in standard fluid intake when *clinical* signs of pulmonary fluid overload are present in combination with echocardiography evidence of left heart enlargement (see appendix). Significant fluid restriction (< 120 ml/kg) is not recommended, as this could lead to a nutritional deficit.

Diuretics

The use of diuretics is recommended when fluid restriction alone is not effective in reducing the *clinical* signs of pulmonary fluid overload. Loop diuretics might have additional benefits in improving lung water clearance over thiazide diuretics, but loop diuretics are associated with increased PDA patency. Data on diuretics are limited and based on studies from an era with significantly different perinatal care. Spironolactone has beneficial extra renal effects in adults with chronic heart failure. Adverse effects of diuretics should be closely monitored.

*Open label treatment, NSAID*

Open label treatment after the 2 courses of study drug is not allowed during this study

*Open label treatment, paracetamol*

In recent years there have been reports on the effect of paracetamol on PDA closure rates.13 Until more high quality data is available, paracetamol has not been recommended for routine clinical use, and the use of paracetamol is discouraged in this study. If the use of paracetamol has already been established in local unit policy and guidelines, the use of standard doses of paracetamol (15 mg/kg iv or oral for 5 days) before surgical ligation is allowed.

*Open label treatment, surgical ligation*

Surgical ligation should be considered if there is a PDA with moderate to large volume shunt in an infant with failure to thrive, progressive clinical and echocardiography signs of heart failure and who is unable to wean from significant respiratory support despite optimal treatment for fluid overload and chronic lung disease. These are the standard indications for ligation of a PDA in most neonatal units currently. The Toronto criteria are recommended for triaging patients with a persistent PDA who are considered for surgical ligation (see appendix).14

*Cardiac ultrasound schedule*

Cardiac ultrasounds are performed according to standard PDA management guidelines, with additional study scans at randomization (begin of study scan) and at transfer or discharge (end of study scan). In addition the uPDA trial will require a brief cardiac ultrasound to confirm ductal patency or closure each 2 weeks. Standard PDA management guideline scans are at clinical diagnosis, before and after each course of study drug and/or open label treatment, and at clinician’s discretion.

*Cardiac ultrasound image protocol*

A minimum imaging protocol includes parameters of ductal size and flow pattern, parameters of effective systemic blood flow (flow pattern in the descending aorta) and parameters of pulmonary volume load (left atrium and ventricular size or volume, left-to-right ventricular output ratio, left pulmonary artery end diastolic velocity). Guidelines and definitions for each of these ultrasound measurements will be provided in a manual to participating units.

Additional ultrasound parameters (conventional Doppler, tissue Doppler, speckle tracking analysis) are collected in units trained for these additional measurements.

*Sample size*

The calculated sample size needed using a non-inferiority design (death or CLD incidence 43%, accepting 10% difference, alpha 5%, beta 20%) is 594 patients.

The John Hunter Children's Hospital admits approximately 70 eligible infants per year, and currently around 1/3 would receive treatment and thus expected to reach inclusion criteria. The Royal North Shore Hospital admits approximately 50 eligible infants per year, with similar treatment rates. Recruitment rates in both centers with previous hemodynamic studies were over 80%. With the intended 2 year duration for this pilot study, an estimated 70 infants could be included and analyzed. As no study thus far has explored NSAIDs with supportive care versus supportive care alone in the management of a PDA, we feel that this sample will be enough to provide data that can help decide on continuing the study as a larger multi-center trial. Our successful collaboration with several similar sized neonatal units in Australia with interest in hemodynamics and the capability of providing cardiac ultrasounds will help complete the full sample size after further funding has been obtained.

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**Study Flow diagram**

Preterm infants < 29 week gestation

Cardiac ultrasound scan schedule

at start of study (<72h of age)

before and after each course of study drug

every 2 weeks until closure

before surgical ligation is considered

before transfer or discharge

Consider surgical ligation in an infant with failure to thrive, with progressive clinical and

echocardiography signs of heart failure, and who is unable to wean from significant respiratory support despite optimal treatment for fluid overload and chronic lung disease

Continue and optimise supportive care if the PDA remains large after the second course of study drug until criteria for surgical ligation are met

Supportive care in both arms; optimised end expiratory pressure and careful fluid management

Repeat study drug if PDA > 1.5 mm is found on cardiac ultrasound 24-48 h after first course

Cardiac ultrasound scan before 72 hours

Exclusion; significant haemorrhage, major congenital abnormalities, other NSAID contraindications

PDA > 1.5 mm

NSAID, 3 doses

Placebo, 3 doses

**Appendix: clinical and ultrasound findings associated with heart failure**

Clinical signs of pulmonary volume overload

Increasing number of apnea’s over the last few days

A persistent (>12-24 hours) increase in FiO2

Increase in mean airway pressure to maintain a stable blood gas

Increasing respiratory distress (respiratory rate, work of breathing) not otherwise explained

Unable to wean of respiratory support not otherwise explained

The need for mechanical ventilation not otherwise explained

Clinical signs of congestive heart failure (enlarged liver, tachypnea, edema)

A murmur, bounding pulses or wide pulse pressure should not be considered signs of pulmonary volume overload

Echocardiography signs of volume overload

Enlarged left atrium

M mode LA/Ao ratio > 1.5

2D Long axis LA diameter/ Aorta annulus diameter ratio > 1.9

LA volume > 1.5 ml/kg

Enlarged left ventricle

LV sphericity (diameter/length) > 0.60

LV end diastolic volume > 3.0 ml/kg

Parameters of high pulmonary blood flow

LPA end diastolic velocity > 20 cm/s

Parameters of increased pulmonary to systemic blood flow

LVO:RVO ratio or Ao Vmax : Pv Vmax > 1.25

LVO:SVC flow ratio > 4.0

Increased pressure loading of the left ventricle

IVRT < 55 msec

Ee’ ratio > 15 (TDI) or > 6 (STE)

EA ratio > 1.0

**Appendix: Toronto criteria for triaging patients for surgical ligation**

**Clinical criteria**

Must be interpreted in the setting of a PDA and the absence of sepsis/NEC

*Category 1*

Profound pulmonary haemorrhage with significant oxygenation difficulty (OI >15 or MAP >12 and FiO2 >0.5)

Low cardiac output syndrome or rapidly progressive cardiorespiratory failure requiring 2 or more inotropic agents

*Category 2*

Deteriorating respiratory status (OI >15 or MAP >12 and FiO2 >0.5)

Preterm born at <26 weeks’ gestation with a large, hemodynamically significant PDA in whom medical treatment is contraindicated

Low cardiac output syndrome or cardiorespiratory failure requiring 1 or more inotropic agents

Neonate with NEC and a large PDA believed to be a significant contributor to clinical instability

*Category 3*

Inability to extubate or wean from respiratory support

Cardiac failure associated with failure to thrive

**Echocardiography criteria**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **A.PDA diameter** | **B.Pulmonary over circulation** | **C.Systemic hypoperfusion** |
| **Moderate volume shunt**  **(A+B and/or C)** | 1.5-3.0 mm with unrestrictive pulsatile flow  (Vmax < 2 m/s) | At least 2 of the following:  LA:Ao 1.5-2.0  IVRT 45-55 ms  EA ratio < 1.0  LVO 300-400 | Absent diastolic flow in at least 2 of the following:  Abdominal aorta  Celiac trunk  Middle cerebral artery |
| **Large volume shunt**  **(A+B+C)** | > 3.0 mm with unrestrictive pulsatile flow  (Vmax < 2 m/s) | At least 2 of the following:  LA:Ao > 2.0  IVRT < 45ms  EA ratio > 1.0  LVO > 400 | Reversed diastolic flow in at least 2 of the following:  Abdominal aorta  Celiac trunk  Middle cerebral artery |