Pia Härkin

CLOSURE OF PATENT DUCTUS ARTERIOSUS IN VERY PRETERM INFANTS

POTENTIAL ROLE OF PARACETAMOL AND CONSEQUENCES OF CURRENT TREATMENTS
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Potential role of paracetamol and consequences of current treatments

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Abstract
The ductus arteriosus connects the pulmonary artery and the descending aorta in the foetus. In normal neonatal transition, the ductus closes soon after birth. If the duct remains significantly open after birth, it may complicate the recovery of a very preterm infant. Present treatments of patent ductus arteriosus (PDA) are either medical (ibuprofen or indomethacin) or surgical (ligation). However, these treatments can have serious side effects, especially in the most immature infants. This doctoral thesis studied the potential role of intravenous paracetamol for PDA treatment in very preterm infants born before 32 weeks of gestation. Consequences of the PDA treatments in an epidemiological birth cohort were also studied. In retrospective Study I stated that treatments of PDA decreased after the introduction of IV paracetamol for early pain management in preterm infants. Study II showed in a randomised clinical trial for the first time that paracetamol has a biological effect on the ductus arteriosus in preterm infants soon after birth. The ductus closed significantly earlier in the paracetamol group than in the placebo group. The epidemiological cohort Study III showed evidence that both medical and surgical treatment of PDA associated with severe bronchopulmonary dysplasia in infants born very preterm. Additionally, surgical PDA ligation was associated with increased risk of necrotising enterocolitis and intraventricular haemorrhage. Study IV showed that treatment of PDA was not associated with increased mortality, even in the most immature preterm infants born before 28 weeks of gestation.

Keywords: cohort study, morbidity, paracetamol, patent ductus arteriosus, PDA epidemiology, PDA treatment, very low gestational age infant
Härkin, Pia, Hyvin pienen keskosen avoimen valtimotiehyen sulka. Parasetamoli-
hoidon merkitys ja nykyhoitojen sivuvaikutukset
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Tiivistelmä

Valtimotiehyt on sikiöaikana avoimena oleva suoni, joka yhdistää keuhkovaltion laskevaan
aortaan ja ohjaaa vähähappisen veren istuukkaan. Yhdessä soikean aukon kanssa suoni takaa siki-
ön verenkierron normaalin toiminnan ennen keuhkojen avautumista. Mikäli valtimotiehyt jää
syntymän jälkeen pitkittyneesti auki, muuttaa se keskosen verenkiertoa siten, että osa aortan
verenkiertoa ohjautuu keuhkoverenkiertoon vaikuttaen pienien keskosen toipumista. Nykyhoido-
toina käytetään joko lääkkeellistä (ibuprofeeni tai indometasiini) tai kirurgista sulkaa. Lääkkeel-
linen hoito ei ole kovin tehokas kaikista epäkypsimmillä keskosilla ja hoitoihin liittyy vakavia-
kin sivuvaikutuksia.

Väitöskirjassa tutkittiin parasetamolilääkityksen vaikutusta hyvin pienen keskosen avoimen
valtimotiehyen sulkeutumiseen. Epidemiologisessa osiossa tutkittiin nykyhoitojen sivuvaikutuk-
sia hyvin pienillä keskosilla. Osatyössä I todettiin, että avoimen valtimotiehyen hoidon tarve
vähenee merkittävästi sen jälkeen kun parasetamoli oli otettu käyttöön kivun hoidossa vastasynty-
neiden teholla. Osatyö II oli satunnaistettu ja sotkoutettu hoitotutkimus, jossa todettiin alkupe-
räishavaintona, että parasetamolilla on biologinen vaikutus keskosen avoimeen valtimotiehyyn.
Parasetamolia saaneilla keskosilla valtimotiehyt sulkeutui aikaisemmin kuin verrokeilla. Hoidol-
lta ei todettu merkittäviä sivuvaikutuksia. Osatyössä III ja IV tutkittiin kaikkien vuosina
Lääkehoidolla (ibuprofeeni ja indometasiini) ja kirurgisella hoidolla todettiin olevan yhteys kes-
kosen kroonisen keuhkotaudin (BPD) vaikeimpaan muotoon. Kirurgisella hoidolla oli yhteys
keskosen vaikeaan suolitulehduskseen ja vaikeaan aivosuodannuotoon. Kuolleisuuden riskin ei
kuitenkaan todettu lisääntyneen valtimotiehyyn hoitoihin liittyen.

Asiasanat: avoimen valtimotiehyyn hoito, avoin valtimotiehyt, hyvin pieni keskonen,
kohorttitutkimus, kuolleisuus, parasetamoli
To my family
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Pia Härkin
Abbreviations

AA  arachidonic acid
APAP  acetyl-para-aminophenol
BW  birth weight
BNP  brain natriuretic peptide
BPD  bronchopulmonary dysplasia
CI  confidence intervals
CLD  chronic lung disease
COX  cyclooxygenase
DA  ductus arteriosus
ECHO  echocardiography
ELGA  extremely low gestational age (< 28 weeks)
GA  gestational age
hsPDA  hemodynamically significant patent ductus arteriosus
IV  intravenous
IVH  intraventricular haemorrhage
LA/Ao  left-atrium-to-aorta ratio
LPA  left pulmonary artery
MCA  middle cerebral artery
MPA  main pulmonary artery
NAPQI  N-acetyl-p-benzoquinone-imine
NDI  neurodevelopmental impairment
NEC  necrotising enterocolitis
NSAID  non-steroidal anti-inflammatory drug
NNT  number needed to treat
NT-proBNP  amino-terminal pro-B-type natriuretic peptide
OR  odds ratio
PAH  pulmonary arterial hypertension
PDA  patent ductus arteriosus
PG  prostaglandin
PGE₂  prostaglandin E₂
PLCS  post-ligation cardiac syndrome
PROM  premature rupture of the foetal membranes
PVL  periventricular leukomalacia
RCT  randomised controlled trial
RDS  respiratory distress syndrome
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<tr>
<td>ROP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>small for gestational age</td>
</tr>
<tr>
<td>VLGA</td>
<td>very low gestational age (&lt; 32 weeks)</td>
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List of original articles

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

The rate of preterm birth varies globally, occurring in 5–18% of all births and contributing significantly to infant mortality and morbidity (Blencowe et al., 2012). Prematurity is the largest cause of neonatal death worldwide (Kong et al., 2016; Liu et al., 2016). The risk for mortality and morbidity is highest in infants born extremely preterm, under i.e. less than 28 weeks of gestation (EXPRESS Group et al., 2009; Serenius et al., 2014). Mortality and morbidity rates of very preterm infants differ between regions and countries (Boghossian, Geraci, Edwards, & Horbar, 2018; Bonet et al., 2017; Edstedt Bonamy et al., 2018; Serenius et al., 2014).

Level of immaturity is the main contributing factor to later neonatal morbidity, such as retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), and bronchopulmonary dysplasia (BPD). However, the importance and the independent role of the patent ductus arteriosus (PDA) in the later management and survival of preterm infants are controversial and unclear. Therapies used for the closure of PDA are either medical (ibuprofen or indomethacin) or surgical, but these therapies have potential side effects for premature infants (R. I. Clyman & Chorne, 2007; Janz-Robinson et al., 2015; Madan, Kendrick, Hagedorn, Frantz, & National Institute of Child Health and Human Development Neonatal Research Network, 2009). There is no consensus regarding either the criteria of hemodynamically significant patent ductus arteriosus (hsPDA) or the optimal postnatal age of treatment (Jain & Shah, 2015; Skelton, Evans, & Smythe, 1994; Zonnenberg & de Waal, 2012).

Previous case reports and observational studies have shown that paracetamol may be an alternative to the closure of PDA (Allegaert, 2013; Aminoshariae & Khan, 2015; Hammerman et al., 2011; Oncel et al., 2013). Several recent randomised controlled trial (RCT) studies also show that paracetamol may be as effective as ibuprofen and indomethacin for closing PDA of preterm infants, but with fewer side effects. However, evidence of the indications, dosage, effectiveness, and safety—including the long-term effects of paracetamol—are still incomplete or lacking.
2 Review of the literature

2.1 Physiology and pathophysiology of the ductus arteriosus

Patency of the ductus arteriosus (DA) is essential in the foetal period, as it connects the main pulmonary artery (MPA) to the descending aorta (Ao) to guarantee normal foetal circulation and development of the foetus. The DA diverts ventricular output away from the lungs and towards the placenta (Hamrick & Hansmann, 2010). Closure of the duct during the foetal period may lead to foetal demise. In normal situations, the duct acts like a physiological shunt and closes functionally by 72 hours of age in 90% of term infants (Gentile et al., 1981; Skinner, Skinner, Alverson, & Hunter, 2000). Normally, the shunt pattern changes left to right before complete closure (Skelton et al., 1994). In normal functional closure of PDA, the wall of the vessel thickens, endothelial cells activate, and smooth muscle cells contract. Vasodilatory agents drop (the main vasodilator is PGE2) and contracting agents (e.g., oxygen level) rise, resulting in the vessel contracting functionally (Hamrick & Hansmann, 2010). In normal situations, after functional closure, the anatomical (final) closure takes place within three weeks of age. In most preterm infants, the functional closure of PDA is immature and delayed.

If the DA remains open for a prolonged period after birth, it can change from a physiological to a pathophysiological shunt, or PDA. Prolonged patency of the duct can be caused by structural, functional, immature, and altered physiological conditions (Bokenkamp, DeRuiter, van Munsteren, & Gittenberger-de Groot, 2010). Because there is normal individual variation of neonatal cardiovascular physiology and circulation changes during the transition period, the hemodynamic diagnostics during the early postnatal time is challenging (Vrancken, van Heijst, & de Boode, 2018). After normal postnatal decrease of high pulmonary pressure, the shunt direction soon changes from right to left (foetal circulation) and becomes left to right (from the aorta to the pulmonary artery) also in immature infants. Normally, the shunt is diverted completely or predominantly in 95% of preterm infants by 5 hours after birth in infants born under 30 gestation weeks (Kluckow & Evans, 2000b). If PDA stays hemodynamically significantly open (hsPDA), it may lead to overloading in the right side (pulmonary overcirculation) and systemic hypoperfusion in the left side (low systemic blood flow) (R. I.
Clyman, 2012). This change in circulation may induce symptoms in the infant condition.

The right-side overloading via the ductal shunt may lead to pulmonary problems, including prolonged need of mechanical ventilation, surfactant inhibition, pulmonary oedema or haemorrhage and later, the risk of BPD and death (Kluckow & Evans, 2000a). On the left side, systemic hypoperfusion may lead to end-organ hypoperfusion and ischemia as a result of reduced renal and mesenteric flow, reduced middle cerebral artery blood flow velocity, and, thereafter, possible risk for NEC, IVH and periventricular leukomalacia (PVL) (Evans & Iyer, 1994; Evans & Kluckow, 1996; Evans, 2015; Pladys et al., 2001). Large PDA can sometimes lead to cardiac failure, but this, fortunately, is rare. Association of PDA with later morbidities is not clear however, and does have great individual variability. Comorbidities depend on the size of PDA, the degree of immaturity, and the capacity of the compensatory mechanisms of the infant’s hemodynamic system. For example, when cerebral autoregulation is disturbed, the risk for IVH with PDA rises (Perlman, Hill, & Volpe, 1981; Van Bel, Van de Bor, Stijnen, Baan, & Ruys, 1989). Even large PDA with low systemic blood pressure combined with good cerebral autoregulation, does not necessarily influence the infant’s prognosis. However, the single or independent role of PDA and its relationship to later morbidities is not clear (Hamrick & Hansmann, 2010).

2.2 The incidence of patent ductus arteriosus (PDA)

In healthy term infants, the incidence of PDA is between 0.02% and 0.006% of live births, with a 2:1 female-to-male ratio (Tripathi, Black, Park, & Jerrell, 2013). The aetiology is suggested to be multifactorial, with some genetic component in the pathogenesis (Bokenkamp et al., 2010; Tripathi et al., 2013). In preterm infants, the occurrence of PDA is inversely related to gestational weeks. The more premature the infant, the higher the incidence of PDA. In very low gestational age (VLGA) infants (born < 32 weeks), more than 30% have PDA, and in those born under 28 weeks, 55–70% are at risk for significant open ductus requiring treatment (Reller, Rice, & McDonald, 1993). However, spontaneous closure is frequent. By 7 days of life, about 80% of infants born between 26 and 31 gestational weeks had no or only small PDA (Van Overmeire, Van de Broek, Van Laer, Weyler, & Vanhaesebrouck, 2001). In contrast, in the group of infants born <25 gestational weeks, the proportion of spontaneous closure was only 12.5%,
showing that the most immature infants are at the highest risk for PDA (Koch et al., 2006).

2.3 Diagnosis and definition of hemodynamically significant PDA

2.3.1 Echocardiography (ECHO)

Colour Doppler heart echocardiography (ECHO) is used to measure the hemodynamic significance and the volume of the ductal shunt (ductal size). ECHO should be performed prior to closing the duct to reveal possible congenital heart defect (Chu, Li, Kosinski, Hornik, & Hill, 2017) and related contraindications for ductal closure. In case of ductal-dependent systemic or pulmonary circulation, closing the duct can be life threatening for the infant. In this case, prostaglandin analogues must be infused to keep the ductal vessel open.

The parameters and ECHO criteria for hsPDA are variable (Jain & Shah, 2015). There are criteria and scoring of hsPDA, but without clear consensus (A. El-Khuffash et al., 2015; Sehgal, Paul, & Menahem, 2013; Skelton et al., 1994; Su, Watanabe, Shimizu, & Yanagisawa, 1997). ECHO parameters commonly used for hsPDA include PDA diameter (the internal size of the duct in two-dimensional view > 1.5-2.0 mm or 2 mm/kg), the left-atrium-to-aortic root ratio (LA/Ao > 1.4), internal ductal diameter > 50% wider than that of the left pulmonary artery, velocity of the shunt < 2 m/s, and a flow pattern characterised by a large left-to-right ductal shunt (Evans & Iyer, 1994; Skinner et al., 2000; Zonnenberg & de Waal, 2012). In clinical practice, evaluating ductal flow and the vessel’s true diameter is challenging because vessel dimensions vary (diameter is not static) during the transitional period, especially in the most immature infants. There is also anatomical and topological variance in the ductal architecture and viewing three-dimensional structures in two-dimension ECHO requires experience and expertise (Krichenko et al., 1989). Left-side (atrial or ventricular) dilatation indicates that the ductus is hemodynamically significant. Large PDA for prolonged time may lead to heart failure. Pressure gradient across PDA shows a continuous flow profile from left to right, indicating a possible large-volume shunt (Evans & Iyer, 1994; Skinner et al., 2000). Experienced echocardiographers and paediatric cardiologists employ other detailed ECHO parameters, such as pulmonary vein Doppler measurements and pulmonary overcirculation measurements from left ventricular output overload. In
large/moderate-volume ductal shunt systemic hypoperfusion (low systemic blood flow), signs can be seen from absent or reversed diastolic flow from the middle cerebral artery, the descending aorta, or/and the coeliac trunk artery (A. F. El-Khuffash, Jain, & McNamara, 2013).

2.3.2 Clinical diagnosis of hsPDA in very preterm infants

The clinical criteria and symptoms of hsPDA in premature infants are classified as a murmur, cardiopulmonary distress, hyperdynamic precordium, bounding pulses, increased need for respiratory support, and wide pulse pressure. A PDA murmur is continuous if there is a constant pressure gradient in both the systole and the diastole as blood is forced via the duct from left to right (from the aorta into the pulmonary artery). The aortic blood pressure must be higher than the pulmonary pressure during diastole to cause the left to right shunt direction in the ductal flow. McNamara’s criteria combine clinical signs and ECHO parameters (McNamara & Sehgal, 2007). Another scoring system for PDA defines the significance of PDA based on ECHO criteria (A. El-Khuffash et al., 2015). The challenge with these definitions is that there is still no consensus for clinicians regarding hsPDA criteria, which PDA should be treated, when, and how. In addition, the great individual variation in premature infants’ hemodynamical adaptance to the PDA shunt makes the criteria for treatment challenging for the clinician. Decisions about therapy should be based on individual clinical signs of a large left-right shunt with echocardiographic parameters showing hsPDA. Chest x-ray may also show signs of increased pulmonary vasculature and notable heart dilatation in the case of hsPDA.

2.3.3 Postnatal age of ductal ECHO screening for treatment

There are different approaches regarding the optimal postnatal age for ECHO screening and the subsequent treatment procedures for PDA in preterm infants. Potential approaches to PDA management are early screening, early targeted intervention, or delayed intervention, which indicates a more conservative attitude. Early screening (before day 3 of life) in extremely low gestational age (ELGA) infants was associated with lower in-hospital mortality (number needed to treat (NNT) to prevent one death = 23), but there were no differences between major neonatal morbidities such as NEC, severe BPD, or severe cerebral lesions when compared to unscreened infants (Roze et al., 2015). Performed on second
postnatal day, cardiac ultrasound-targeted measures of PDA diameter and maximum flow velocity in very preterm infants showed that a specific PDA severity score is able to predict the later occurrence of chronic lung disease (CLD) or death in the high-risk group (A. El-Khuffash et al., 2015). Early screening entails a risk of overtreatment of PDA and a possible higher risk for adverse effects associated with the treatment procedures. Early targeted intervention of ductal closure is based mainly on shunt volume, and its benefits are the selection of patients with an evolving shunt. The later or delayed (conservative) intervention approach is based mainly on clinical assessment, and entails less need for treatment but also a potential risk for later morbidity (risk for BPD) and mortality associated with PDA itself.

2.3.4 Biochemical markers

Brain natriuretic peptide (BNP) and amino-terminal pro-B type natriuretic peptide (NT-proBNP) are synthesised and released into the circulatory system by the cardiac ventricular myocytes in response to pressure overload, volume expansion and increased myocardial wall stress. Because the hemodynamic efficient of PDA is occasionally difficult to comprehend with a sole ECHO, a simple blood test would provide an attractive additional diagnostic tool for clinicians. Unfortunately, studies have shown that the diagnostic accuracy of BNP and NT-Pro-BNP for hsPDA are not valid for clinical decisions in the management of hsPDA of premature infants (M. Kulkarni et al., 2015).

2.4 Treatment of PDA

2.4.1 Treatment challenges

Medical treatment with either indomethacin or ibuprofen and surgical closure (PDA ligation) is the mainstay in the management of PDA. Of late, conservative management has become a more popular choice of treatment. There is no consensus of treatment (Evans, 2015), which reflects the holistic problem of reconciling PDA in preterm infants with the continuing dilemma of diagnosing and defining hsPDA. The Effective Perinatal Intensive Care in Europe (EPICE) study (a population-based cohort study in 19 regions in 11 European countries during 2011-2012 of all births born before 32 gestational weeks) noticed that
treatment policies of PDA treatments were very heterogenic. However, the variation in PDA treatment did not explain differences in patient risk factors such as mortality and severe BPD (Edstedt Bonamy et al., 2017). The independent role of PDA and its association with later morbidities is not clear, and a more uniform strategy is needed. The treatment of PDA is challenging as spontaneous closure is frequent, and the solid evidence of treatment benefit is lacking. PDA treatment trials (randomised controlled studies of PDA treatment) have not shown evidence of a reduction in PDA-associated morbidities such as severe IVH, NEC, severe BPD, death, and worsened neurodevelopmental outcome (Benitz, 2010; Benitz, 2012; R. I. Clyman & Chorne, 2007). The treatment of PDA and, especially the early active closure of PDA and its association with later neonatal morbidity remains inconclusive (A. El-Khuffash et al., 2015; Gudmundsdottir et al., 2015; Schena et al., 2015; Slaughter, Reagan, Bapat, Newman, & Klebanoff, 2016; Weisz, More, McNamara, & Shah, 2014). The EPICE study showed that the proportion of PDA treatments varied from 10% to 39% (p < 0.001) between (European) regions, indicating different management approaches (Edstedt Bonamy et al., 2017).

2.4.2 Conservative management of PDA

The conservative treatment option means watchful waiting for spontaneous closure of PDA. Recently, the trend of conservative management has become more accepted approach (Benitz & Committee on Fetus and Newborn, American Academy of Pediatrics, 2016). It has been shown that routine treatment to close PDA, either medically or surgically, in the first two weeks after birth does not improve long-term outcomes (level of evidence: 1A) (Benitz & Committee on Fetus and Newborn, American Academy of Pediatrics, 2016). Neither clinical trials nor meta-analyses have shown that closing the duct improves long-term outcomes. Routine treatment, especially when conducted early on, has no effect on morbidities like BPD, NEC, and mortality (Benitz, 2010). Prophylactic indomethacin (given by 12 hours of life) seems to reduce the rate of severe IVH and early severe pulmonary haemorrhage, but it did not improve long-term neurodevelopmental or respiratory outcomes (Schmidt et al., 2001). Jhaveri et al. (2010) reported a significantly lower rate of NEC in ELGA infants without treatment of PDA (conservative management) when compared to infants treated with early ligation after an attempt of indomethacin therapy (Jhaveri, Moon-Grady, & Clyman, 2010). In a recent meta-analysis of different treatment options
for hsPDA (ibuprofen, indomethacin, paracetamol or placebo), placebo or no treatment was not associated with an increased likelihood of mortality and morbidity such as NEC or IVH (Mitra et al., 2018). On the contrary, a multicentre cohort study of the most preterm infants (born < 1000 g, included infants n=494) showed that a conservative approach towards PDA was associated with higher mortality, whereas a surgical approach was associated with an increased occurrence of BPD at 36 weeks and ROP. However, medical and conservative treatments were protective for the outcome of death/BPD at 36 weeks (Sadeck et al., 2014).

High fluid intake (> 170 mL/kg/day) during the first days of life in very premature infants has been associated with an increased risk of PDA (Stephens et al., 2008). Fluid restriction has been shown to predispose closure of the ductus, thus constituting an important part of conservative PDA management. Optimal fluid restriction in VLGA infants improves pulmonary function by decreasing the overloading of pulmonary circulation (De Buyst, Rakza, Pennaforte, Johansson, & Storme, 2012). In a systematic review, restricted fluid intake is associated with a reduction in PDA (E. F. Bell & Acarregui, 2008). When the fluid volume is restricted, adequate energy intake must be evaluated to ensure sufficient calorie intake and avoid harming the premature infant’s optimal outcome. In practice, this means adding energy supplies such as carbohydrates, protein, and fat to the diet to prevent growth restriction.

The use of diuretics is not recommended for the treatment of PDA because there is no evidence of benefits to PDA closure. Furthermore, side effects of these drugs, especially to premature infants in their early days, could present more drawbacks than advantages (Brion & Campbell, 1999; Ketkeaw, Thaithumyanon, & Punnahitananda, 2004; B. S. Lee et al., 2010).

### 2.4.3 Medical treatment of PDA

Medical treatments for PDA closure in preterm infants include the cyclooxygenase (COX) inhibitors ibuprofen and indomethacin. These drugs are non-steroidal anti-inflammatory drugs (NSAIDs) that contract the duct by inhibiting the formation of vasodilators such as prostaglandins (PGs) (Figure 1). Inhibition occurs when the drugs influence the cyclooxygenase enzyme and block the formation of PGs (mainly PGE2) from arachidonic acid (AA) (R. I. Clyman, Saha, Jobe, & Oh, 2007; Ohlsson, Walia, & Shah, 2015; Sadeck et al., 2014). Treatment success is about the same (70–80%) for both ibuprofen and
indomethacin (Gournay et al., 2004). ELGA infants, in whom the occurrence of hsPDA is highest, present the most challenging and problematic group for medical treatment. The efficiency of the drug is generally worse in ELGA infants than in more mature infants. Furthermore, due to immaturity, the frequencies of other comorbidities, and the risks of side effects due to treatments are higher in these high-risk infants. Another dilemma is that a meta-analysis of more than 50 RCT studies found no long-term benefits regarding NSAID treatments in preterm infants (Benitz, 2010; Benitz, 2012).

**Indomethacin**

Indomethacin is an NSAID that inhibits COX enzymes and prevents the formation of PGs from AA (Figure 1). It was first described in 1976 for the closure of PDA in premature infants (Friedman, Hirschklau, Printz, Pitlick, & Kirkpatrick, 1976; Heymann, Rudolph, & Silverman, 1976). Indomethacin is the most widely used COX-inhibitor for PDA closure until now. Slightly different dose regimens, varying between 0.1 and 0.2 mg/kg every 24-hours and usually for three doses have been used to treat PDA (Mezu-Ndubuisi et al., 2012). A prolonged course (> 4 doses) has also been used, but a large meta-analysis of 431 infants noticed no difference in PDA closure, re-treatment or ligation rates when compared to a short course. Furthermore, there was an increased risk for NEC, RR 1.87 (95% CI 1.1–3.27), in groups in which prolonged indomethacin courses were administrated (Herrera, Holberton, & Davis, 2007).

Early prophylactic indomethacin has been shown to reduce periventricular or intraventricular haemorrhage but does not improve later neurodevelopmental outcome. In a multicentre double-blinded RCT trial, infants born before 29 weeks of gestation with large PDA (“high-risk group”) were randomised to receive either indomethacin (n=44) or a placebo (n=48). Infants were screened by ultrasound and the study drug was started by 12 hours of age (prophylactic treatment). Infants in the indomethacin group had significantly less pulmonary haemorrhage (2% vs 21%) and a trend of less IVH (4.5% vs 12.5%), but the latter was statistically not significant. The infants with small PDA (not randomised infants) had a lower risk of pulmonary haemorrhage, and 80% of those had spontaneous PDA closure, indicating that an early and precise diagnosis of ductal shunt volume is important when making the decision about therapy (Kluckow, Jeffery, Gill, & Evans, 2014). Indomethacin treatment is associated with renal impairment (Lin et al., 2017) and gastrointestinal complications; the risk being
even stronger if an infant is simultaneously receiving corticosteroids or nephrotoxic drugs (e.g., aminoglycosides). In a RCT study of extremely low birth weight infants with significant PDA, the indomethacin group (n=73) received the dose 0.2+0.1+0.1 mg/kg every 24 hours as compared with the ibuprofen group (n=71) which received the dose 10+5+5 mg/kg every 24 hours. Indomethacin was more effective than ibuprofen at closing PDA (66% vs 49%, p=0.046). However, renal side effects were more common in the indomethacin group (e.g., higher creatinine, lower glomerular filtration, lower urinary output) than in the ibuprofen group. There was no difference in other neonatal morbidities (BPD, IVH, NEC, and ROP) or mortality between the groups (Lin et al., 2017).

Ibuprofen

Ibuprofen is a nonselective COX-inhibitor that reduces PG-mediated vasodilatation (Figure 1). It is administered intravenously or orally, and various dosing regimens have been proposed. The standard dose of ibuprofen is given over three days (three doses): 10 mg/kg/day followed by 5 mg/kg/day at 24-hour intervals for two days (IV and oral administrations) (Van Overmeire, Touw, Schepens, Kearns, & van den Anker, 2001). Higher doses comprise 15–20 mg/kg followed by 7.5–10 mg/kg administered every 12 to 24 hours for a total of three doses (IV and oral); repeated courses have also been used (Dani et al., 2012; Mitra et al., 2018).

There is some evidence that orally administered ibuprofen is as effective as IV ibuprofen for PDA closure (Ohlsson et al., 2015; Oncel & Erdevci, 2016). When compared, oral ibuprofen was as efficacious as IV indomethacin in closing PDA, and easier to administer (Aly et al., 2007). In a meta-analysis (68 RCT studies with 4,802 infants), the effects of indomethacin, ibuprofen and paracetamol to close hsPDA were studied. A high dose of oral ibuprofen was associated with the highest likelihood of hsPDA closure, versus standard doses of IV ibuprofen or IV indomethacin (Mitra et al., 2018). However, high-dose ibuprofen presents a higher risk of potential side effects, especially in the most immature infants. Because of the nonselective mechanism of COX-inhibitors, ibuprofen can cause side effects that include gastrointestinal bleeding, NEC and pulmonary hypertension. Risks for gastrointestinal side effects are greater when ibuprofen is combined with cortisone treatment (Peltoniemi et al., 2005). The risk for pulmonary arterial hypertension (PAH) following ibuprofen treatment is highest in low gestational age infants and when prenatal risk factors such as small
for gestational age (SGA), maternal hypertension of pregnancy or oligohydramnion are present (Kim et al., 2016). However, ibuprofen generally has a better safety profile when compared to indomethacin (Ohlsson et al., 2015).

### 2.4.4 Surgical ligation of PDA

Surgical ligation of PDA is effective in definitively interrupting the ductal shunt. Most premature infants who require surgical treatment for PDA are the most immature (less than 28 gestational weeks) and the sickest, typically with hemodynamic instability and respiratory insufficiency. Most have had medical treatment (NSAID) prior to ligation if there has been no contraindication for medical treatment, such as IVH (Weisz & Giesinger, 2018). The past 10 years have seen a reduction in ligation rates due to a more conservative approach of treating PDA (Benitz & Committee on Fetus and Newborn, American Academy of Pediatrics, 2016) and the concern of side effects related to the procedure. However, treatment options vary globally between centres and countries. In the United States, for example, direct surgical ligation in ELGA infants has been more frequent than in the United Kingdom (A. Kulkarni, Richards, & Duffy, 2013). There is also great variability between centres: California hospital ligation numbers range from 0% to 67% (H. C. Lee, Durand, Danielsen, Duenas, & Powers, 2015).

While effective, ligation has been associated with both short and long-term adverse neonatal outcomes, including post-ligation cardiac syndrome (PLCS), vocal fold paralysis, pneumothorax, chylothorax, and later neurosensory impairment in early childhood (A. F. El-Khuffash, Jain, Weisz, Mertens, & McNamara, 2014; Gould et al., 2003; Ibrahim et al., 2015; Jhaveri et al., 2010; Ting et al., 2016; Weisz et al., 2014). The independent role of ligation and its association with later problems are unclear; because ligated infants are usually the most immature and the sickest, the causality to adverse outcomes is unsure. Most ligated immature infants have one or several related morbidities simultaneous with prematurity, such as respiratory distress syndrome (RDS) (with mechanical ventilation), IVH, BPD, ROP and NEC, and therefore the independent role of PDA and its treatment in later morbidity and mortality is not clear, and causality is difficult to show. Thus, a selection bias may exist in studies that compare ligated and non-ligated infants and their later outcomes. There are also studies where ligation (either direct or after failed medication therapy) has not been associated with increased mortality or neurodevelopmental impairment (NDI).
when compared to conservative management alone (Weisz et al., 2018). In some studies, mortality rates in ligated group have been associated with a lower risk of in-hospital mortality (Weisz et al., 2018). On the other hand, surgical ligation in VLGA infants seemed to increase the risk of BPD, ROP laser treatment, longer hospital stay, and longer mechanical ventilation when compared to un-ligated group (Youn, Moon, Lee, Lee, & Sung, 2017).

Different results show the heterogeneity of the issue and the difficulty of demonstrating cause-consequence of the ligation and later outcomes, especially in retrospective and epidemiological studies. However, PLCS after ligation has been associated with both a higher risk of mortality and a risk of neurodevelopmental problems later. PLCS may worsen hemodynamic instability and oxygenation (A. F. El-Khuffash et al., 2014). The optimal selection of patients and the timing of ligation are key to minimising the procedure’s side effects. The careful selection of patients for PDA ligation and systematic triage has been shown to reduce the number of PDA ligations (24% of referrals for surgery were cancelled) without impacting short-term neonatal morbidity (Resende et al., 2016).

### 2.4.5 Other options for the treatment

Percutaneous or catheter-based closure has been used to treat PDA for more than 50 years in term neonates (Portsmann & Wierny, 1978). However, the success and safety of this treatment in very preterm infants is unclear, and has not become treatment of choice. The procedure has potential future value for premature infants because it may have fewer complications than surgical ligation. Risks defined in catheter-based closure are acute arterial injury and aortic or left pulmonary artery (LPA) obstruction (Backes et al., 2016; Zahn et al., 2016). In a retrospective analysis performed over a 10-year period at a single centre (n=52), PDA closure in very preterm infants weighing less than 4 kg was successful in 88% of the infants. In extremely premature infants (n=24) the successful rate for transcatheter closure of PDA was also 88% (3/24 failed) (Zahn et al., 2016). A less invasive procedure is an attractive alternative over surgical ligation, but more studies are still needed.
2.5 Postnatal age for PDA treatment

The optimal postnatal age for PDA closure is unclear. The timing of medical treatment has ranged from prophylactic and early treatment at the very first postnatal days to later treatment at several weeks or even months of age.

2.5.1 Prophylactic and early treatment

Prophylactic treatment of PDA refers to closure of the ductus before 12–24 hours of life and before the onset of symptoms in all at risk preterm infants. Previous trials of prophylactic indomethacin and ibuprofen seemed to decrease the risk of PDA but caused significant side effects and did not decrease overall morbidity and mortality (Gournay et al., 2004; Kluckow et al., 2014; Schmidt et al., 2006). Although prophylactic indomethacin has been shown to reduce the rate of severe (grades 3 and 4) IVH and pulmonary haemorrhage, it has not demonstrated a reduction in later morbidities such as BPD, ROP, and NEC, and no improvement in survival (Schmidt et al., 2006). Indomethacin treatment of large PDA (> 1.7 mm) before 12 hours of age reduced the incidence of pulmonary haemorrhage (9% vs 23%) and the need of later treatment of PDA (20% vs 40%) but had no effect on the primary outcome of death or adverse cranial ultrasound findings (Kluckow et al., 2014). A meta-analysis of prophylactic IV indomethacin found no improvement in long-term neurodevelopmental outcome or mortality (Fowlie, Davis, & McGuire, 2010; Schmidt et al., 2001). Prophylactic ibuprofen treatment has also been tested in preterm infants. Unfortunately, the significantly increased risk of pulmonary hypertension was found to associate with this approach. Prophylactic ibuprofen treatment has since been abandoned (Gournay et al., 2004). In conclusion, prophylactic medical treatment for PDA is not recommended because of its side effects and because it poses no benefit for later morbidity and mortality (Cotts, 2009; Ohlsson & Shah, 2011).

Prophylactic or early ligation is not considered a valid treatment for the same reason and has been abandoned. If surgical closure is performed early, when a premature infant’s hemodynamic system is both fragile and labile, the risks for complications rise both during and after the operation. Surgical closure of PDA may induce a rapid increase in previously low cerebral perfusion as a result of shunting blood to pulmonary circulation. This, in combination with the fragile vasculature of the germinal matrix and the potential for reperfusion injury, is likely to predispose the infant to IVH (Soleymani, Khoo, Noori, & Seri, 2015).
One strategy to prevent hsPDA is early treatment to close the duct very soon after its diagnosis. In this approach, drug treatment is started before 7 days of life. Because there is no evidence of benefits, this approach is not recommended by most neonatologists. Early ibuprofen treatment (median age of 3 days) in VLGA infants did not have any benefits over delayed treatment (Sosenko, Fajardo, Claure, & Bancalari, 2012). A standard dose of IV ibuprofen therapy within 72 hours of birth in ELGA infants was effective to close the duct but resulted in no benefits in later outcomes (e.g., NEC, IVH, BPD, and ROP) (Aranda et al., 2009).

2.5.2 Late treatment (symptomatic therapy)

The criteria and postnatal age for late treatment vary, but late treatment refers to treatment after 7 days of life. This approach allows for possible spontaneous closure of the open ductus. The treatment is usually started after hsPDA symptoms appear or if there is a criterion of hemodynamic significance in ultrasound. Conservative treatment sometimes refers to treatment even after discharge. Studies have shown that surgical ligation in VLGA infants before 14 days of life increases the rates of ROP laser treatment, BPD, longer hospital stay and longer mechanical ventilation when compared to the non-ligated group (Gudmundsdottir et al., 2015; Youn et al., 2017).

2.5.3 Optimal postnatal age for treatment

The hsPDA should be closed, but what is the optimal time for closure? Premature closure should be avoided, as possible side effects from the treatments are usually greater than the shunt effect. The current evidence does not support prophylactic or early (presymptomatic) closure. At the earliest, the ductal shunt should be closed after it has turned completely left-to-right. In the case of pulmonary hypertension (right-to-left shunt) or a ductal cross shunt (pulmonary and systemic pressure of about the same magnitude), closing the duct can lead to right ventricular failure. The optimal postnatal age for active ductal closing after the shunt flow has turned remains controversial. Different trials are inconclusive regarding when to treat the open ductus, as closing the duct has not affected the outcomes of other severe neonatal morbidities (e.g., severe BPD, ROP, NEC, and IVH). The majority of hsPDA cases appear in ELGA infants, who frequently develop moderate-to-large PDA. Premature closure should be avoided because of the risk for complications from the treatments, and too-late closure can increase
the risk for morbidities associated with left-to-right shunt. A trial of early vs late ibuprofen treatment without hsPDA resulted in otherwise similar outcomes, but early ibuprofen treatment was associated with worse respiratory outcome (Bancalari, 2016; Bancalari & Jain, 2017; Sosenko et al., 2012).

The individual approach may be the most valid approach for treating PDA. Treatment choice and postnatal age at treatment should be based on a pathophysiology-based approach, where the clinical signs of hsPDA, ECHO signs of hsPDA, and the possible side effects of treatments are evaluated and weighed. The main dilemma of optimal closing time is that even if the duct is actively closed, causality to morbidities associated both with the ductal shunt and the therapies is unclear. Because of the heterogeneity of studies and protocols, it is difficult to show the long-term benefits of the single therapies. Therefore, the precise optimal time for treatment is challenging to determine. If the ductal shunt is small and without harm to the infant, it favours conservative management, but if it is large and causes severe symptoms such as ventilator problems, pulmonary haemorrhage or hemodynamic lability, it should be closed. Premature and routine treatment should be avoided; instead an individual approach should be employed to evaluate the individual compensatory mechanisms of hemodynamics.

2.6 Paracetamol (acetaminophen)

2.6.1 Paracetamol for pain in preterm infants

Paracetamol (acetaminophen or N-acetyl-p-aminophenol, APAP) is an antipyretic NSAID used to treat mild to moderate pain in premature infants. Like COX - inhibitors, the drug inhibits the conversion of arachidonic acid (AA) to prostaglandins (PGE\textsubscript{2}, PGI\textsubscript{2}). Paracetamol acts by lowering cyclooxygenase products, but the precise mechanism of its action is unclear (Lucas, Warner, Vojnovic, & Mitchell, 2005).
Fig. 1. Ibuprofen, indomethacin, and paracetamol in the arachidonic acid pathway. COX- inhibitors ibuprofen and indomethacin inhibit the cyclooxygenase (COX) part of prostaglandin. Paracetamol inhibits the peroxidase moiety of the enzyme, decreasing prostaglandin synthesis. Both sides must be active in the prostaglandin synthase enzyme to have the catalysing action.

Paracetamol may also inhibit the descending serotonergic pathways and inhibit prostaglandin synthesis in the central nervous system. It also may have an active metabolite influence on cannabinoid receptors (Pacifici & Allegaert, 2014). A simplified model of the effect of paracetamols on the AA pathway is shown in Figure 1. Unlike ibuprofen and indomethacin, paracetamol acts on the peroxidase region of the prostaglandin synthase enzyme, resulting in a decrease in PG synthesis (Anderson, 2008; Veyckemans, Anderson, Wolf, & Allegaert, 2014). Paracetamol is primarily eliminated by hepatic metabolism, and hepatic maturation is the key in paracetamol pharmacokinetics. Paracetamol undergoes both sulfation and glucuronidation, and these nontoxic products are excreted renally. In neonates, the sulfation of paracetamol predominates. Paracetamol also undergoes oxidation by cytochrome P450 (CYP) enzymes, predominantly CYP2E1, to form the reactive N-acetyl-p-benzoquinone-imine (NAPQI), which is detoxified by conjugation with glutathione (Figure 2) (Cook, Roberts et al., 2016; Cook, Stockmann et al., 2016). Repeated paracetamol administration has no effect on glutathione plasma levels in the preterm infant, potentially reflecting good glutathione stores.
In preterm infants, sulfation predominates, while the proportion of glucuronidation increases later in childhood and adults. Paracetamol is metabolised primarily in the liver into nontoxic* and toxic** products. Nontoxic products have renal excretion, while toxic NAPQI binds to liver proteins and amino acids. NAPQI production is primarily metabolised by the CYP2E1 pathway, and liver toxicity depends on NAPQI levels, not paracetamol itself.

In studies of paracetamol pharmacokinetics of premature infants, the dose of paracetamol depends of the gestational age, but patient size (weight) is the major covariate of clearance variance in neonates (Allegaert, Palmer, & Anderson, 2011). Volume distribution in premature infants at 27 gestational weeks is 0.64 L/Kg, reaching the mature value at about 6 months of age (0.4–0.45 L/kg). The increased volume of distribution in neonates supports the use of a larger initial dose (loading dose) of 20 mg/kg intravenously to attain paracetamol threshold concentration sooner (10–20 mg/L) (Veyckemans et al., 2014; Wang et al., 2013). After the loading dose, the maintenance dose is given, usually a repeated dose of 7.5–10 mg/kg/q6h. The clearance of paracetamol in neonates is one-third of the mature value reported in adults. Clearance maturation is slow until 40 weeks of gestation and matures rapidly to reach 90% of adult capacity in the first year of life (Allegaert et al., 2011; Allegaert, Naulaers, Vanhaesebrouck, & Anderson, 2013; Pacifici & Allegaert, 2014; Wang et al., 2013). However, precise data

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**Fig. 2. Paracetamol (acetaminophen) metabolism main pathways. In preterm infants, sulfation predominates, while the proportion of glucuronidation increases later in childhood and adults. Paracetamol is metabolised primarily in the liver into nontoxic* and toxic** products. Nontoxic products have renal excretion, while toxic NAPQI binds to liver proteins and amino acids. NAPQI production is primarily metabolised by the CYP2E1 pathway, and liver toxicity depends on NAPQI levels, not paracetamol itself.**
regarding the pharmacodynamic of paracetamol in the most immature infants are still limited.

### 2.6.2 Paracetamol for patent ductus arteriosus

The use of paracetamol for closure of PDA in preterm infants was first published in a small case report in 2011 (Hammerman et al., 2011). In that study, oral paracetamol was given to five premature infants, after which all ducts closed. Following this promising study, many observational studies were published, showing that paracetamol could be an alternative for the closure of PDA in preterm infants (Oncel et al., 2013; Terrin et al., 2016). Thereafter in prospective RCT studies, paracetamol has been noted to have a closing effect on the DA in premature infants (Dang et al., 2013; El-Mashad, El-Mahdy, El Amrousy, & Elgendy, 2017; Oncel et al., 2014). Unlike indomethacin and ibuprofen, paracetamol has no peripheral vasoconstrictive effect and has fewer side effects (e.g., gastrointestinal). It would thus provide a more attractive choice for closure of PDA than indomethacin and ibuprofen.

Primarily, paracetamol is administered to preterm infants intravenously. The general dose used to treat PDA (15 mg/kg/6q) is greater than that used for pain and antipyretics (7.5–10 mg/kg/6q). The efficacy of paracetamol has been compared to COX-inhibitors, and it has been noted to be comparable with indomethacin and ibuprofen. Both IV and oral paracetamol have been compared to placebo and COX-inhibitors (IV indomethacin, IV or oral ibuprofen). Paracetamol has been shown to be as effective as COX-inhibitors ibuprofen and indomethacin, but with fewer side effects (El-Mashad et al., 2017; Oncel et al., 2013; Terrin et al., 2016). Oral and IV paracetamol have been shown to be equally effective (Dang et al., 2013; Oncel et al., 2014). Although there are challenges in oral route administration in very preterm infants during their first postnatal days, some promising studies have shown that oral administration may be a safe and efficient treatment for PDA (Dang et al., 2013; Oncel & Erdeve, 2016). RCTs have shown that oral paracetamol is as effective as oral ibuprofen for the treatment of PDA in infants born preterm, no significant differences between the secondary outcomes were found (Al-Lawama, Alammori, Abdelghani, & Badran, 2018; Dang et al., 2013; Ohlsson & Shah, 2015; Oncel et al., 2014). However, paracetamol metabolism (e.g., peak concentrations and clearance) has been studied mainly in
IV forms. Because enteral paracetamol metabolism differs from the IV route, dosage and safety of oral paracetamol for PDA need more prospective studies.
Table 2. Randomised, controlled trials of paracetamol for patent ductus arteriosus

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment groups</th>
<th>Study design</th>
<th>Paracetamol dose</th>
<th>Ibu/indo dose</th>
<th>Patients (para/ibu/indo)</th>
<th>Postnatal age drug started</th>
<th>GW Results (ductus closed after first course) n(%)</th>
<th>Main result</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dang 2013</td>
<td>Po para / Po ibu</td>
<td>RCT, not blinded</td>
<td>15 mg/kg/6h Ibu</td>
<td>10+5+5mg/kg for 3 days</td>
<td>160 (80/80) ≤14 d</td>
<td>≤34 Para/ibu 65(81.2%)/63(78.8%) p=0.693, RR 0.83 (0.60−1.15)</td>
<td>Para as effective as ibu</td>
<td>Para has less hyperbilirubinemia and ge-bleeding</td>
<td></td>
</tr>
<tr>
<td>Oncel 2014</td>
<td>po para / po ibu</td>
<td>RCT</td>
<td>15 mg/kg/6h Ibu</td>
<td>10+5+5mg/kg for 3 days</td>
<td>90 (40/40) 48–96 h</td>
<td>≤30 Para/ibu 29(72.5%)/31/(77.5%) p=0.600,RR 0.82 (0.38−1.76)</td>
<td>Para as effective as ibu 2</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>El-Mashad 2016</td>
<td>IV para/ IV ibu/ IV indo</td>
<td>RCT</td>
<td>15 mg/kg/6h Ibu</td>
<td>10+5+5mg/kg for 3 days</td>
<td>100/100/100 ≤14 d</td>
<td>≤28 Para/ibu/indo 80/77/81 p=0.868</td>
<td>Para as effective as ibu and indo</td>
<td>Para has less side effects (renal, platelet count, ge bleeding)</td>
<td></td>
</tr>
<tr>
<td>Yang 2016</td>
<td>po para / po ibu</td>
<td>RCT</td>
<td>15 mg/kg/6h Ibu</td>
<td>10+5+5mg/kg for 3 days</td>
<td>87 (44/43) 15 h−10 d</td>
<td>≤37 Para/ibu 31(70.5%)/33/(76.7%) p=0.506</td>
<td>Para as effective as ibu</td>
<td>In para group less oliguria (2.3% vs14.0%), ns p=0.108</td>
<td></td>
</tr>
</tbody>
</table>

1Ten infants died (5/5 per group) before completing the treatment. 2Reopening rate was higher in the paracetamol group, but was not statistically significant (24.1% vs 16.1%) p=0.43. 3Plasma and urine PGE2 levels were lower after treatment in the ibuprofen group as compared to the paracetamol group.
Serum concentrations of paracetamol should be about 10−20 mg/L to have antipyretic and analgesic effect (Allegaert et al., 2013; Wang et al., 2013). Therapeutic paracetamol levels for closure of the ductus are unknown. In one small (n=10) retrospective pilot study of hsPDA closure with enteral paracetamol treatment (15 mg/kg 4 times/day for 3 days) in premature infants (less than 34 weeks), a higher paracetamol concentration correlated with short-term ductal response. If the concentration was below 20 mg/L, there was no response in PDA, showing that the concentration needed to close PDA might be higher than the target used for pain (Bin-Nun, Fink, Mimouni, Algur, & Hammerman, 2018). Further studies are needed to define a precise dose of paracetamol used for treating PDA.

2.6.3 Side effects of paracetamol

Acute and short-term safety of paracetamol is well documented. The drug is known to have possible acute side effects on the liver. Especially when administrated in high doses, elevations of liver enzymes have been seen. Fortunately, the true hepatotoxicity caused by paracetamol is rare in neonates. It is generated through the production of N-acetyl-p-benzoquinone-imine (NAPQI) by the hepatic cytochrome P450 (Allegaert et al., 2011; Palmer et al., 2008). Paracetamol-induced hepatotoxicity is not associated with exposure to the drug per se but depends more of the amount of exposure to NAPQI and the amount of protecting agent glutathione stores. In an extreme case report, a premature infant born at 25 gestational weeks had accidentally received more than a 30- to 60- fold overdose of paracetamol (446 mg/kg IV). An antidote (a glutathione precursor, N-acetylcysteine) was given, and the infant survived without side effects (Porta, Sanchez, Nicolas, Garcia, & Martinez, 2012). One hypothesis for the lack of acute paracetamol toxicity in preterm infants is that, due to their immaturity, the production of toxic metabolites (NAPQI) in the liver is low, while the synthesis of protecting agents such as glutathione in the liver is mature, and thus formation and stores are good despite prematurity.

Recent studies suggest a potential association between maternal paracetamol exposures and possible foetal and, later, postnatal side effects for children. Safety data concerning the long-term side effects of paracetamol use in the neonatal period are limited. Epidemiological studies have shown that the maternal use of analgesics in the second trimester or later could be associated with male reproductive disorders such as cryptorchidism or hypospadias (Fisher et al., 2016;
A possible explanation may be that this affects steroidogenesis and, consequently, results in reduced androgen (testosterone) production in the foetal testes. In-utero paracetamol side effects were stronger if exposure occurred during the second trimester and if the mother was taking the drug for a long term (> 4 weeks). However, the current evidence regarding foetal exposure to paracetamol and later male reproductive disorders cannot be concluded directly. The effect of paracetamol use, both in the neonatal period and later in childhood, on the male testis is unknown.

There is no solid evidence that paracetamol could close the foetal duct when administered in high (even toxic) doses (Taney, Anastasio, Paternostro, Berghella, & Roman, 2017). There is one case report of ductal closure in near-term infants due to maternal self-medication with nimesulide and paracetamol (Simbi, Secchieri, Rinaldo, Demi, & Zanardo, 2002). The possible association between paracetamol use during pregnancy and later adverse neurodevelopmental outcomes has risen in recent studies (Bauer, Kriebel, Herbert, Bornehag, & Swan, 2018). Previous animal studies have shown that the presence of paracetamol, during the critical period of brain development in mice induced long-lasting effects on cognitive function (Philippot, Gordh, Fredriksson, & Viberg, 2017; Viberg, Eriksson, Gordh, & Fredriksson, 2014). However, ibuprofen exposure during brain growth spurt did not affect brain development in mice (Philippot, Nyberg, Gordh, Fredriksson, & Viberg, 2016; Philippot et al., 2017). In humans, a recent review of prenatal paracetamol exposure and later neurodevelopmental development showed an increased risk of adverse neurodevelopmental outcome. The association was shown between foetal paracetamol exposure and increased risk for later ADHD and hyperactivity. The problems with these studies are the heterogeneity of the protocols and in their outcomes, and therefore the difficulty to prove causality exists. Paracetamol, which is considered a safe medication for pain and fever during pregnancy, is the most commonly used medication in pregnancy (Werler, Mitchell, Hernandez-Diaz, & Honein, 2005). As it is also widely used in term and preterm infants (Allegaert & van den Anker, 2017), further research on its safety is urgently needed.

### 2.7 Association of the treatments of PDA with neonatal morbidities

It is unclear which is worse: the prolonged left-to-right shunt through PDA that causes circulatory changes or the side effects of the therapies. The strength of the side effects of NSAIDs medications must be weighed against very rapid surgical
ductal closure and its consequences on the circulation of very preterm hemodynamically labile and fragile infants (Abdel-Hady, Nasef, Shabaan, & Nour, 2013; Evans & Iyer, 1994; Evans, 2015; Gudmundsdottir et al., 2015; Noori, 2010). The problems of these cause-consequences associations are even more challenging in extremely premature infants, as later morbidities may simply be consequences of prematurity itself (Laughon, Simmons, & Bose, 2004).

2.7.1 Associations with bronchopulmonary dysplasia (BPD)

The pathophysiology of BPD is multifactorial. The independent role of PDA and the causality of its treatments with the risk of BPD is unclear. Previous studies have suggested that PDA can contribute to the development of BPD by increasing the fluid filtration to the lungs, thus causing pulmonary oedema and an increased need for ventilator support (Noori, 2010). A former epidemiological study of VLGA infants found a slight increase in the odds of BPD in infants with PDA (Marshall et al., 1999). However, some studies show an association between severe BPD and treatments for PDA. EPICE, a large European population-based study (n=6896), indicated that preterm infants (born under 31 weeks) who had treatment for PDA were at higher risk of BPD or death in all regions around Europe, with an adjusted RR 1.33 (95% CI 1.18–1.51), than those who were not treated. Survival without major neonatal morbidity was not related to PDA treatment, demonstrating that variations in PDA treatments did not explain the result. The incidence of BPD in 23– to 26-week gestational age infants was lower in cases of expectant management for PDA than when PDA was treated with either indomethacin or ligation (Sung et al., 2016). However, in the Trial of Indomethacin Prophylaxis in Preterms (TIPP) study, the risk of BPD in infants treated with prophylactic indomethacin was similar when compared to placebo. Furthermore, in the TIPP study, the incidence of BPD was higher after prophylactic indomethacin than after placebo treatment in infants without PDA (Schmidt et al., 2006). Indomethacin implicates oliguria and fluid retention, potentially predisposing premature infants to lung oedema. This side effect must be considered when giving NSAID medications to very preterm infants. It has been shown that sole fluid restriction has no effect in reducing BPD but does have an effect in reducing PDA. In a systematic review comparing restricted fluid intake and liberal fluid intake, less fluid was associated with reduction in PDA, but there was only a trend towards a lower risk of BPD, RR 0.85 (0.63–1.14) (E. F. Bell & Acarregui, 2008). Surgical ligation (prophylactic, primary, or secondary)
was also associated with an elevated risk of BPD (R. Clyman, Cassady, Kirklin, Collins, & Philips, 2009; R. I. Clyman, 2013). In summary, active closure of PDA has not been shown to reduce the risk of BPD, indicating an unclear association the shunt of PDA and the risk of BPD.

2.7.2 Associations with other neonatal outcomes and mortality

COX-inhibitors have acute side effects, such as oliguria and risk of gastrointestinal perforation that are described in greater detail in section 2.4.3. Associations between the treatment of PDA and later neonatal morbidity have been described. An association has been suggested between ibuprofen and indomethacin and neonatal morbidities like ROP, NEC, and BPD (R. I. Clyman & Chorne, 2007; Irmesi, Marcialis, Anker, & Fanos, 2014). An association between surgical ligation and later neurodevelopmental impairment has been described (Ibrahim et al., 2015; Sadeck et al., 2014). Surgical ligation after indomethacin therapy has also been associated with NEC when compared to a conservative approach (Jhaveri et al., 2010). However, the potential for ELGA infants to succumb directly because of PDA or its treatments is rare (Patel et al., 2015).
3 Aims of the research

Patent ductus arteriosus in preterm infants is one of the very important problems in neonatal medicine. There are differences in both the definition and the treatment strategies of hsPDA. COX-inhibitors and the ligation of PDA are established therapies. In this thesis, we wanted to determine whether paracetamol has the potential to become a novel treatment for PDA. After observational studies on the association between paracetamol treatment and the incidence of PDA, we attempted to explore whether paracetamol treatment for pain has a biological effect on PDA. The currently available medical therapies and surgical ligation have side effects in premature infants. We aimed to consolidate and extend these observations using a national cohort of very preterm infants. The specific aims of the research were:

- To study, in a retrospective trial, whether the introduction of paracetamol for the treatment of pain in VLGA infants with respiratory distress would influence the incidence of PDA (Study I).
- To study in a prospective randomised trial (RCT), whether paracetamol has a biological effect on the early constriction of open DA in premature infants (Study II).
- To study the adverse effects of paracetamol used in the early treatment of preterm infants (II).
- To study the predisposing factors for PDA in VLGA infants in a national cohort (Study III).
- To study the adverse effects of the therapies used for PDA closure in a large epidemiological study during the first hospitalisation (Studies III and IV)
- To study the mortality of ELGA infants during the first hospitalisation period and its possible associations to PDA (Study IV).
4 Patients and methods

4.1.1 Paracetamol for patent ductus arteriosus (I and II)

Study I

This retrospective study consists of 105 VLGA infants and 96 VLGA control infants born before 32 gestation weeks admitted to the Oulu University Hospital neonatal intensive care unit (NICU). The paracetamol group infants were born between June 2009 and December 2011, and controls were born from January 2008 to May 2009. Infants with lethal malformations, chromosomal defects, or severe congenital infections were excluded. Paracetamol was introduced originally for VLGA infants’ mild and moderate pain in June 2009. Intravenous (IV) paracetamol was given to infants before 72 h of age (Perfalgan® 10 mg/ml solution for infusion, Bristol-Myers Squibb Finland, Espoo, Finland) The first loading dose of paracetamol was 20 mg/kg, followed by 7.5 mg/kg maintenance dose every 6 h. Paracetamol was given if there were clinical signs of pain, which were systematically screened with the neonatal infant acute pain assessment scale (NIAPAS). If the patient did not improve after starting paracetamol, IV morphine was available. Paracetamol was stopped when no signs of pain were observed during 24 h.

Heart echo was performed on postnatal days two to five. PDA criteria included a significant left-to-right shunt with signs of hemodynamic distress (left-atrium-to-aorta ratio >1.30, tachycardia or high pulse pressure) and persistent respiratory distress. The size of PDA was measured as internal ductal calibre vs pulmonary artery main branch root calibre. PDA was treated with a general course of IV ibuprofen (10 mg/kg/day, then twice 5 mg/kg/day) which was repeated once if necessary. Surgical closure of PDA was performed when ibuprofen was not effective or was contraindicated. The closure of PDA was determined by cardiac ultrasound. Moderate to severe BPD was diagnosed at 36 weeks of gestation using the oxygen weaning test, IVH was defined based on the international schedule of Papile with several ultrasound exams, and NEC grade 2 to 3 was defined as described by Bell (M. J. Bell et al., 1978; Papile, Burstein, Burstein, & Koffler, 1978; Walsh et al., 2004). Accurately recorded data on paracetamol dosages, ibuprofen, surgical ligation, and known side effects of paracetamol were obtained from the NICU patient database, Centricity Critical
Care Clinisoft (GE Healthcare Finland, Helsinki, Finland). These data were reviewed with Crystal Reports XI software (SAP Finland Oy, Espoo, Finland). Permission to use the hospital databases was given by the administrative chief of Oulu University Hospital. Statistical analyses were performed using the PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Continuous variables were analysed using the independent samples t-test and dichotomous variables using the two-tailed Chi-squared test. A multivariate analysis of factors influencing the risk of PDA was performed by logistic regression. Significance was set at $p<0.05$.

**Study II**

This study was a randomised, double-blinded, phase I–II trial (The Premature Infants’ Paracetamol Study, PreParaS study) with the aim of establishing a new paracetamol indication in high-risk preterm infants. The study group consisted of VLGA infants (born < 32 gestational weeks) born in the Oulu University Hospital NICU between September 18, 2013 and January 2, 2015. Infants requiring intensive care were randomly assigned to the IV paracetamol or the placebo (0.45% NaCl) group (Figure 3). The study was performed in accordance with Good Clinical Practice guidelines. The hospital ethics committee and the Finnish Medicines Agency (Fimea) approved the protocol. The monitoring officer oversaw the trial arrangements regularly. This trial was assigned to the European Clinical Trials Database (EudraCT 2013-008142-33) and the ClinicalTrials.gov registry (NCT01938261).
**Randomisation and intervention**

Infants were randomised to either the IV paracetamol or the placebo group (IV 0.45% NaCl). Computed randomisation was done using a 4-block design. To decrease the risk of significant heterogeneity between cases and controls, individual treatment strata were defined by gender and immaturity. All staff (nurses and doctors treating patients) were blinded to the study medication. The dose of paracetamol used for pain in neonates, included a first loading dose of 20 mg/kg, followed by 7.5 mg/kg every 6 h for 4 days, given in 15-minute infusions.
The study drug was started before 24 hours of age. No other paracetamol was
given before, during, or 2 days after (washout period) the study protocol.

**Cardiac ultrasound (ECHO)**

The first cardiac ultrasound was performed after recruitment but before the study
drug was started. After the study drug was administrated, ECHO was performed
daily until one day after the study medication was finished. Thereafter, in infants
with open DA, cardiac ultrasound to measure ductus calibre was performed once
or twice a week. All infants were examined at the time of discharge from NICU.
The ECHO was performed by neonatologists (n=3) who were trained by
paediatric cardiologist to enhance the uniformity of evaluations. Altogether, 330
ultrasound examinations were performed to study the infants. An interrater
reliability analysis for the 3 raters was calculated using the Cronbach’s α statistic
to determine consistency among raters. Patients were examined in the supine
position with slight left shoulder recumbences. The recordings were obtained
using Vivid i® (first eight patients) or Vivid S5® (GE Healthcare, Helsinki,
Finland) ultrasound devices with appropriate transducers (12S or 6S). No sedation
was used during the ECHO examinations. In cases where the infant was
distressed, the neonatal nurse soothed the infant, and oral 20% glucose solution
drops were administered if needed. ECHO parameters defined were ductal
internal calibre (mm) from the narrowest point of the duct from the pulmonary
side of the vessel and the left-atrium-to-aorta ratio (LA/Ao) from M-mode. The
smallest diameter of the ductal pulmonary end was measured from the
parasagittal plane of the high left parasternal window (ductal view). Diagnostic
criteria of hsPDA were internal ductal diameter > 50% wider than the left
pulmonary artery, LA/Ao ratio >1.4, and flow patterns showing a large left-to-
right ductal flow shunt.

**Outcomes and statistics**

The primary outcome was the decrease and closure of the ductus during the
intervention as a function of postnatal age. The secondary outcomes were: LA/Ao
ratio, the age of permanent closure of the ductus, treatment for ductus, the side
effects of paracetamol, neonatal morbidity, and mortality. Paracetamol
concentrations were analysed from serum samples stored at -70° C using the
Paracetamol Assay Kit. All samples were analysed as duplicates. The inter- and
intra-assay coefficients of variation were 18.1% and 14.1%, respectively. Paracetamol concentrations were stable after prolonged storage.

Adverse effects such as low blood pressure and need of inotropes and laboratory values like platelets, serum sodium, and bilirubin were recorded. Renal function was monitored from urinary output (mL/kg/hour). Clinical symptoms of hsPDA were murmur, prolonged ventilation, increased pulse pressure, cardiomegaly, active precordium and bounding pulses. If PDA required closure, the decision was made by a clinician. Options for treatment were ibuprofen and surgical closure.

**Statistical analysis of Study II**

Sample size assumed a 40% proportional difference between groups. It was assumed that the ductus calibre would diminish during the study medication period in 50% of the paracetamol-treated infants and 10% of the controls. In power 80%, alpha-error 0.05 sample size was calculated to be 48 patients. Outcomes were analysed as the intention to treat. The Mann-Whitney U-test or the samples t-test was used for continuous variables and the Chi-squared test for categorical values. Ductal closure postnatal ages were estimated using the Kaplan-Meier analysis and the hazard ratios were calculated using the Cox regression analysis. RANOVA (repeated measures analysis of variance) was used to assess the daily variation in ductal fluid balance between the groups. Statistical analysis was performed using IBM SPSS version 22.0 for Microsoft Windows (IBM Acquires SPSS Inc., Chicago, IL, USA).

**4.1.2 Morbidities and mortality associated with PDA treatments (III)**

The study data were based on the Finnish Medical Birth Register of preterm infants born before 32 gestational weeks (22–31). Data consisted originally of 4,143 VLGA infants born during the years 2005–2013 (Figure 4). Exclusion criteria were lethal congenital malformation, lethal chromosomal defect, or death before 7 days of postnatal age.
PDA treatments, morbidities and mortality, and other risk factors were recorded from birth until discharge, or until the age of 42+0 postconceptional weeks. The final study population consisted of 3,668 infants (Figure 4). Diagnosis of hsPDA was based on the same clinical and echocardiographic criteria mentioned in the methods for Study I and Study II. The definition of small for gestational age (SGA) was based on reference values for normal growth in premature infants in the Finnish population (Sankilampi, Hannila, Saari, Gissler, & Dunkel, 2013). The duration of gestation was evaluated by ultrasound examination at an estimated 16 weeks of gestation. The diagnosis of ROP was based on international guidelines (International Committee for the Classification of Retinopathy of Prematurity, 2005), and NEC was diagnosed on the basis of Bell criteria (M. J. Bell et al., 1978), stages II and III being recorded. IVH grades were defined as described by Papile (Papile et al., 1978). Severe IVH was defined as
being stage 3 or 4. Mild BPD (grade 1) was diagnosed based on the need for supplementary oxygen or assisted ventilation at 28 postnatal days. If the infant required less than 30% of supplementary oxygen at 36 weeks of gestation (±6 days), the oxygen reduction test was performed to define grade 2 (moderate) BPD (Walsh et al., 2004). Severe BPD (grade 3) was diagnosed if the infant required at least 30% oxygen or assisted ventilation to reach a saturation level of 90–96% at the age of 36 gestational weeks (±6 days). Due to incomplete data for grade 2 BPD, only severe BPD (grade 3) was included in the final analysis (Table 3).

Inotrope use was recorded if IV inotropic agents (dopamine, dobutamine, and/or noradrenaline) were administered. Respiratory support was defined in case of either invasive ventilation (conventional or high-frequency oscillatory ventilation [HFOV]) or non-invasive ventilation, which were recorded. Non-invasive ventilation was recorded when nasal continuous positive airway pressure or a high-flow nasal cannula was needed. All mortalities during the first hospitalization were recorded up to postconceptional age 42+0 weeks.

Statistical analysis of Study III

A logistic regression analysis, with and without adjustment for gestational age at birth (weeks), intrauterine growth (SGA), delivery hospital, and antenatal steroids, was performed to evaluate the effect of early neonatal morbidity (RDS, need for inotropes, surfactant therapy or mechanical ventilation) on the risk of PDA requiring treatment. Multivariate logistic regression, with a forward stepwise variable selection procedure was used to identify the most effective set of predictors of early neonatal morbidity. A prior multivariate analysis of the multicollinearity of the predictors used in the univariate analysis was performed using a variation inflation factor (VIF). If the VIF of a given predictor was greater than 3, that predictor was eliminated from the multivariate analysis. A logistic regression analysis was also performed to evaluate the associations between the treatments for the closure of PDA and serious morbidities, including severe BPD (grade 3), ROP grades 3–5, NEC stages 2–3, IVH grades 3–4 and death. These morbidities were adjusted with respect to antenatal factors (gestational weeks, SGA, delivery hospital and antenatal steroids) and postnatal factor RDS. In addition, a logistic regression analysis was performed to compare the risk of severe IVH in the case of early (< 7 days) and late ligation. The results of the logistic regression analyses were expressed as odds ratios (ORs), and their 95% confidence intervals (95% CIs). The differences in mean birth weight and
gestational age between the treatment groups were tested with the Student’s \( t \)-test, and differences among more than two groups were evaluated using an analysis of variance (ANOVA), with Tukey’s HSD correction method for post hoc comparisons. Differences in gender distribution were tested by the Chi-square test. All the statistical analyses were performed with IBM SPSS Statistics for Windows, (Version 22.0, IBM Corp, Armonk, NY).

4.1.3 National survival analysis of infants born extremely preterm (IV).

The study data were based on the Finnish Medical Birth Register of preterm infants born 2005–2013 before 28 gestation weeks (22+5 – 27+6) without congenital anomalies. The primary aim of the study was to define the mortality risks of the most premature infants during the first hospitalisation period. The original data consisted of 1,371 ELGA infants (born < 28 gestational weeks). Those infants with lethal malformations or genetic defects were excluded.

Statistical analysis of Study IV

Differences in gender distribution were tested by the Chi square test. The differences in mean birth weight and gestational age were tested with the Student’s \( t \)-test. Mann-Whitney U-test was used to compare medians of skewed distributed continuous variables, like postnatal age of death. Standardized Normal Deviate (SND) test was used to compare the differences in the proportions of neonatal morbidities and mortality between SGA and non-SGA infants. Associations of neonatal morbidities with mortality were evaluated using logistic regression analysis adjusted with antenatal steroids, gestational age at birth and delivery hospital. Analyses were performed separately on SGA and non-SGA infants. The results of the logistic regression analyses were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Postnatal age of demise was evaluated by Kaplan-Meier survival analysis and differences between non-SGA and SGA infants were tested using Log-Rank test. All the statistical analyses were performed with IBM SPSS Statistics for Windows, (Version 25.0, IBM Corp, Armonk, NY).
5 Results

5.1 Paracetamol for patent ductus arteriosus

Study I

This retrospective study showed that the annual incidence of PDA decreased from 30.7% to 14.7% (p=0.008) after the introduction of paracetamol originally given for pain management to VLGA infants in the NICU. After paracetamol administration, there was less medical intervention for PDA (ibuprofen treatment to 15 paracetamol group infants and to 26 controls, p=0.013). Three paracetamol-exposed and 7 control infants required surgery (Table 3). No adverse events were seen. Paracetamol treatment was associated with a lower relative risk for PDA (RR 0.48, p=0.008, Chi-square) and a lower risk for ibuprofen therapy (RR 0.50, p=0.013). Rate of PDA closure by ibuprofen was similar in males and females (81% vs 73%).
Table 3. Characteristics of the groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paracetamol group n=102</th>
<th>Control group n=88</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g (SD)</td>
<td>1201 (379)</td>
<td>1308 (369)</td>
<td>0.051</td>
</tr>
<tr>
<td>Gestation weeks (SD)</td>
<td>28.5 (1.9)</td>
<td>29.0 (2.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Surfactant doses (SD)</td>
<td>1.1 (0.9)</td>
<td>0.9 (0.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ventilation days (SD)</td>
<td>3.3 (7.1)</td>
<td>3.8 (9.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>PDA diagnosis, n (%)</td>
<td>15 (14.7)</td>
<td>27 (30.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ibuprofen treatment, n(%)</td>
<td>15 (14.7)</td>
<td>26 (29.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Surgical ligation, n (%)</td>
<td>3 (2.9)</td>
<td>7 (8.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ductal closure (postnatal day)</td>
<td>11 (20)</td>
<td>15 (41)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

The number of paracetamol doses per patient (mean, SD) was 17 (11.8). The postnatal age (hours, SD) for the first dose was 13.2 (13.7), and the mean duration of paracetamol (days, SD) therapy was 4.3 (3.1), showing that paracetamol therapy was begun as a prophylactic drug very early in postnatal life. Short duration of pregnancy decreased (OR 0.58, 95%CI 0.47−0.71, p<0.001), and paracetamol increased the odds (OR 4.2, 95%CI 1.8−9.7, p=0.001) of closure of PDA.

Study II

This randomised, controlled, and double-blinded study protocol showed for the first time that paracetamol has a biological effect on PDA in very premature infants soon after birth. The DA closed earlier in the paracetamol group than in the control group infants (Figure 5). The protocol of serial cardiac ultrasound examinations (n=330) was performed to all study infants. Interrater reliability (3 examiners) was alpha 0.97 (95%CI 0.90−0.99). Baseline characteristics were similar in both groups (Table 4).
Table 4. Baseline characteristics of the PreParaS study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paracetamol group (n=23)</th>
<th>Placebo group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational weeks, wk (SD)</td>
<td>28.4 (2.4)</td>
<td>28.3 (2.1)</td>
</tr>
<tr>
<td>Birth weight, kg, mean (SD)</td>
<td>1.22 (0.4)</td>
<td>1.12 (0.3)</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>20 (87)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Antenatal steroids, doses/mother, mean (SD)</td>
<td>1.65 (0.9)</td>
<td>1.64 (0.5)</td>
</tr>
<tr>
<td>PROM, n (%)</td>
<td>10 (43)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Cesarean section, n (%)</td>
<td>15 (65)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>13 (57)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Apgar at 5 min age, median (range)</td>
<td>7 (4-10)</td>
<td>6 (2-9)</td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>16 (70)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Surfactant doses per patient, mean (SD)</td>
<td>1.3 (1.3)</td>
<td>1.4 (0.9)</td>
</tr>
</tbody>
</table>

There was no difference in the basic (first measurement) ductal size between groups. The mean (SD) first calibre of internal ductal diameter was 1.57 (0.7) mm in the paracetamol group and 1.4 (0.8) mm in the placebo group (P=0.38). In the paracetamol group, the ductus closed faster at the end of the intervention as compared to the placebo (0.45% NaCl) group. The number of infants with a closed DA was higher in the paracetamol group than in the placebo group (HR 0.49, 95% CI 0.25–0.97, P=0.016. The median (IQR) postnatal age (hours) for the observed ductal closure in the paracetamol group was 41 (33–85), and in the placebo group 78 (50–375), p=0.045. No difference was seen between the LA/Ao ratios (p = 0.31). None of the infants had PDA treatments during the study drug administration. Seven infants (14.6%) had therapy for PDA before their discharge from the NICU. The mean (SD) postnatal age (hours) for ductal closure in infants born after 27 weeks of gestation was 80 (151) in the paracetamol group vs 322 (514) in the placebo group (p=0.004). In the extremely preterm infants group (born < 27 gestational weeks) (n=8), the effect of paracetamol for ductal closure was not seen (p=0.63). Four (50%) of those infants had therapy for PDA (3 in paracetamol group and 1 in placebo group).
Paracetamol was well tolerated, and no acute side effects were seen. Secondary outcomes are listed in Table 5. There was no difference in adverse events nor in neonatal outcomes between the groups. Renal side effects were also not observed. The urinary output during the first week of life was similar (p=0.102), and no difference was seen in oliguria (urine output < 1 ml/kg/h) or polyuria (urine output > 5 ml/kg/h). There was no difference between the groups regarding phototherapy periods and highest bilirubin levels. Furthermore, no signs of paracetamol-induced hypotension were seen as the requirement of inotropes were similar (p=0.74).
Table 5. Secondary outcomes of the PreParaS study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paracetamol group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for PDA, n (%)</td>
<td>4 (17)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Mechanical ventilation, d median (range)</td>
<td>1 (0-32)</td>
<td>2 (0-39)</td>
</tr>
<tr>
<td>Supplemental oxygen, d mean (SD)</td>
<td>20 (24.5)</td>
<td>22.4 (25.0)</td>
</tr>
<tr>
<td>Inotropes, n=0/1/2/3</td>
<td>17/7/0/1</td>
<td>16/5/0/3</td>
</tr>
<tr>
<td>Hypernatremia (&gt;150 mmol/L), n (%)</td>
<td>5 (22)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Phototherapy periods, n mean (SD)</td>
<td>3.5 (1.7)</td>
<td>3.9 (2.0)</td>
</tr>
<tr>
<td>Highest s-bil, µmol/L, mean (SD)</td>
<td>159 (21)</td>
<td>158 (19)</td>
</tr>
<tr>
<td>BPD, gr 2-3</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>IVH gr 1-2, n (%)</td>
<td>5 (22)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Severe IVH, gr 3-4</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>NEC, grade 3, n (%)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ROP treated, n (%)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

1=Inotropes: 0=none, 1=dopamine/dobutamine, 2=dopamine and dobutamine, 3=dopamine, dobutamine and norepinephrine

Paracetamol concentrations were analysed in serum samples (n=87). No toxic level was noticed in paracetamol concentrations (range 0–25.2 mg/L), and no accumulation of drug level was seen during the drug administration period. Mean (SD) concentration during day one was 9.8 (5.5) mg/L (n=26), and the same on day four of the drug administration was 11.8 (6.0) mg/L (n=17, P=0.29). No gender difference was seen in paracetamol levels (boys’ mean (SD) concentration was 9.2 (6.2), while girls’ mean was 9.0 (5.6) mg/L (p=0.91). When the most immature infants were analysed further, those born < 29 gestational weeks did not differ in their concentrations from those born > 29 gestational weeks (9.4 (5.5) vs 8.9 (6.2) mg/L, respectively, P=0.71. In conclusion, paracetamol concentrations did not explain the differences in ductal closures.

5.2 Morbidities and mortality associated with PDA treatments (III)

Original cohort data consisted of 4,143 VLGA infants born in Finland during 2005–2013. Most of the infants (91%) were born in university hospitals, and only 9% were born at local or central hospitals. After exclusion, the final data consisted of 3,668 VLGA infants whose mean gestational age was 29.1 weeks, and the mean birth weight was 1243 g (Table 6). PDA treatment had been
administered to 30.9% of the infants, and of those, the majority (90.1%) had received medical treatment for the closure of PDA. Surgical ligation was performed in 9.9% (362/3668) of the infants. Surgery was the primary treatment in 112 cases, and 250 infants had both medical and surgical treatment (Table 6). In ELGA infants (< 28 weeks), the rate of PDA treatment was three times higher than among infants born at 28 weeks or later (i.e, 619 of 1060 cases required therapy for PDA; 58.4% vs 19.7%).
Table 6. Final study population and treatments of PDA.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No therapy</th>
<th>Medical</th>
<th>Direct Ligation</th>
<th>Both therapies</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2536</td>
<td>N=770</td>
<td>N=112</td>
<td>N=250</td>
<td>N=3668</td>
</tr>
<tr>
<td>Gestational age, week, mean (SD)</td>
<td>29.7 (1.9)</td>
<td>28.3 (2.1)</td>
<td>26.1 (1.9)</td>
<td>26.1 (1.9)</td>
<td>29.1 (2.2)</td>
</tr>
<tr>
<td>Birth weight, kg, mean (SD)</td>
<td>1340 (371)</td>
<td>1115 (336)</td>
<td>834 (297)</td>
<td>846 (278)</td>
<td>1243 (390)</td>
</tr>
<tr>
<td>SGA, n (%)</td>
<td>350 (13.8)</td>
<td>111 (14.4)</td>
<td>20 (17.9)</td>
<td>27 (10.8)</td>
<td>508 (13.8)</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>2368 (94.9)</td>
<td>719 (94.5)</td>
<td>100 (90.1)</td>
<td>242 (98)</td>
<td>3429 (94.9)</td>
</tr>
<tr>
<td>Apgar at 5 min, md(^1) (range)</td>
<td>8 (6-9)</td>
<td>7 (6-8)</td>
<td>6 (5-7)</td>
<td>6 (5-7)</td>
<td>7 (6-8)</td>
</tr>
<tr>
<td>Intubation, n (%)</td>
<td>917 (37.9)</td>
<td>421 (55.5)</td>
<td>105 (95.5)</td>
<td>189 (75.9)</td>
<td>1632 (46.2)</td>
</tr>
<tr>
<td>RDS, n (%)</td>
<td>1394 (55.0)</td>
<td>671 (87.1)</td>
<td>108 (96.4)</td>
<td>239 (95.6)</td>
<td>2412 (65.8)</td>
</tr>
<tr>
<td>Surfactant therapy</td>
<td>1232 (48.6)</td>
<td>632 (82.1)</td>
<td>102 (91.1)</td>
<td>233 (93.2)</td>
<td>2199 (60.0)</td>
</tr>
<tr>
<td>Conventional ventilation, n(%)</td>
<td>1359 (53.6)</td>
<td>658 (85.5)</td>
<td>111 (99.1)</td>
<td>246 (98.4)</td>
<td>2374 (64.7)</td>
</tr>
<tr>
<td>HFOV, n (%)</td>
<td>215 (8.5)</td>
<td>145 (18.8)</td>
<td>75 (67.0)</td>
<td>116 (46.4)</td>
<td>551 (15.0)</td>
</tr>
<tr>
<td>Postnatal steroids, n(%)</td>
<td>186 (7.3)</td>
<td>121 (15.7)</td>
<td>69 (61.6)</td>
<td>104 (41.6)</td>
<td>480 (13.1)</td>
</tr>
</tbody>
</table>

1=median

Postnatal age of the PDA treatments was analysed for different treatment groups. The mean postnatal age (SD) for the first dose of medical treatment was 4.0 (4.1) days, and that of primary surgical ligation was 13.8 (11.4). Of those who had medical treatment followed by surgery, the former was at a mean age of 4.1 (4.7) days of life, and the latter was at 15.7 (12.0). The infants who responded to medical treatment were born later in gestation (mean of 28.3; difference of means of 2.1; 95% CI 1.8–2.4; P<0.001) and had a higher birth weight (mean of 1115 g; difference of means of 336; 95% CI: 227–311; P<0.001) than the nonresponders. Those infants who underwent primary surgical ligation had a mean gestational age of 26.2 weeks (SD 1.9) and a mean birth weight of 834 g (SD 297). However, the infants who did not have PDA therapy had a longer gestation age (29.7 weeks, SD 1.9) and a higher birth weight (1340 g, SD 371) than those that required treatment for PDA (P<0.001 for all three post hoc comparisons). No gender differences were found with regard to the PDA therapies (P=0.212).

Study III stated that RDS and the need for mechanical ventilation were independently associated with the risk of PDA requiring therapy. The severity of lung disease, rather than prematurity per se, was associated with the risk of hsPDA. After adjustment (for gestational weeks, growth restriction, and hospital of birth), odds were to RDS (OR 1.9 95%CI 1.0–3.5, p=0.042) and mechanical ventilation (OR 2.0 95%CI 1.1–3.6, p=0.030). In ventilated infants, however, the
ventilation mode HFOV was independently associated with a decreased risk of PDA after controlling other variables in the model.

The population-based cohort study of VLGA infants also showed that medical and surgical treatment of PDA was associated with the risk of severe BPD (OR: 2.1; 95% CI: 1.4–3.0; P<0.001; and OR: 4.0; 95% CI: 2.0–8.2, P<0.001, respectively). The association was strongest in ELGA infants who required both medical treatment and surgical closure of PDA (OR: 8.2; 95% CI: 3.5–19.1; P<0.001). Primary surgical ligation additionally increased the risk of both severe IVH (OR: 4.3; 95% CI: 2.5–7.3; P<0.001) and grade 2-3 NEC (OR: 2.1; 95% CI: 1.2–3.6; P<0.007). However, medical treatment was associated with lower mortality. Severe ROP (grades 3–5) was not associated significantly with any treatment for PDA. In conclusion both medical and surgical therapies for PDA were associated with severe BPD, and primary surgical ligation was associated with NEC and severe IVH. Furthermore, ligation during the first week of life was associated with a remarkably increased risk of severe IVH relative to later ligation (OR: 4.9; 95% CI: 2.5–9.8; P<0.001). Medical treatment itself and followed by surgery was associated with lower mortality after adjusting for gestational age, intrauterine growth restriction (SGA), delivery hospital, and antenatal steroids.

Table 7 shows the associations of PDA treatments with neonatal morbidity and mortality during the first hospitalisation period. Different treatment groups are compared to infants with no treatment for PDA, and associations are shown as odds ratios (ORs) and their 95% confidence intervals (95% CIs). These results are adjusted for gestational weeks, SGA, delivery hospital, antenatal steroids, and RDS.
Table 7. VLGA infants’ neonatal morbidity and mortality ORs in different PDA treatment groups (compared to no PDA treatment).

<table>
<thead>
<tr>
<th>Outcome/ treatment</th>
<th>All OR 95% CI</th>
<th>P-value</th>
<th>&lt;28 gestation weeks OR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe ROP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>1.1 (0.5-2.4)</td>
<td>0.797</td>
<td>0.9 (0.4-2.1)</td>
<td>0.752</td>
</tr>
<tr>
<td>Ligation</td>
<td>0.6 (0.1-2.9)</td>
<td>0.532</td>
<td>0.3 (0.04-0.2)</td>
<td>0.231</td>
</tr>
<tr>
<td>Both therapies</td>
<td>1.5 (0.6-4.0)</td>
<td>0.399</td>
<td>1.5 (0.6-4.1)</td>
<td>0.388</td>
</tr>
<tr>
<td>Severe BPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>2.1 (1.4-3.0)</td>
<td>&lt;0.001</td>
<td>2.3 (1.3-4.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Ligation</td>
<td>4.0 (2.0-8.2)</td>
<td>&lt;0.001</td>
<td>4.4 (2.0-9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both therapies</td>
<td>5.8 (3.1-11.1)</td>
<td>&lt;0.001</td>
<td>8.2 (3.5-9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEC gr 2-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>1.3 (0.9-1.8)</td>
<td>0.151</td>
<td>1.3 (0.8-2.1)</td>
<td>0.245</td>
</tr>
<tr>
<td>Ligation</td>
<td>2.1 (1.2-3.6)</td>
<td>0.007</td>
<td>2.2 (1.2-3.9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Both therapies</td>
<td>1.4 (0.9-2.3)</td>
<td>0.176</td>
<td>1.4 (0.8-2.3)</td>
<td>0.278</td>
</tr>
<tr>
<td>Severe IVH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>1.1 (0.7-1.6)</td>
<td>0.817</td>
<td>0.9 (0.5-1.5)</td>
<td>0.058</td>
</tr>
<tr>
<td>Ligation</td>
<td>4.3 (2.5-7.3)</td>
<td>&lt;0.001</td>
<td>4.4 (2.4-8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both therapies</td>
<td>1.3 (0.8-2.2)</td>
<td>0.311</td>
<td>1.2 (0.7-2.1)</td>
<td>0.601</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>0.5 (0.3-0.9)</td>
<td>0.011</td>
<td>0.4 (0.2-0.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ligation</td>
<td>1.0 (0.5-1.8)</td>
<td>0.901</td>
<td>0.9 (0.4-1.7)</td>
<td>0.649</td>
</tr>
<tr>
<td>Both therapies</td>
<td>0.3 (0.2-0.7)</td>
<td>0.003</td>
<td>0.3 (0.1-0.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5.3 Mortality of infants born extremely preterm (IV)

The mean gestational weeks (SD) of the data was 25.7 (1.6), and the mean birth weight (SD) was 800 g (225) Treatment of PDA was administered to 47.6% of the infants (644/1353). Surgical ligation was performed on 22.2% of the infants (301/1353), and in those, the direct ligation proportion was 7.0%. Median postnatal age (days) of death in non-SGA infants was 17.6 (range 307), and that in SGA infants was 47.8 days (range 208), p=0.053. During the third day of life, the SGA infants’ proportion for death began to differ from that of normal growth infants, after that, the survival proportion was poorer in SGA infants through the first hospitalization period (Figure 6). After adjustment for antenatal steroids, gestational weeks and delivery hospital growth restriction was a clear independent risk factor for mortality (OR: 4.6; 95% CI: 2.6–8.1; P<0.001).
RDS [OR 2.3; 95% CI (1.0–5.2), P=0.040] and NEC were also associated with higher mortality [OR 4.8; 95% CI (2.9–7.7), P<0.001]. Severe IVH was associated with mortality in non-SGA infants [OR 3.4; 95% CI (1.9–6.0), P<0.001], but not in SGA infants [OR 3.3; 95%CI (0.5–23.0), P=0.232]. When studied further, diagnosis of pre-eclampsia was associated with the lower incidence of severe IVH. Thereafter, maternal pre-eclampsia was associated with lower mortality during the first week [OR 0.5; 95%CI (0.4–0.8), P=0.004], but was not associated after one week of survival [OR 0.6; 95%CI (0.3–1.2), P=0.178].

None of the treatments for PDA associated with the increased mortality of ELGA infants after adjustment. However, medication therapy [OR 0.5; 95% CI (0.3–0.99), P=0.045] and combination therapy [OR 0.3; 95% CI (0.1–0.6), P=0.001] of PDA associated with lower risk of mortality. This association was not seen in direct surgical ligation group [OR 1.1; 95% CI (0.6–2.2), P=0.736]. There was clear difference in causes of death between SGA and non-SGA infants. SGA
infants succumbed to lung diseases (RDS, severe BPD), while NEC and severe IVH were the major causes of death for normal-growth ELGA infants.
6 Discussion

The decision to treat PDA in a very preterm infant should be based on comprehensive clinical and echocardiographic markers of hsPDA. Adequate diagnosis should be based on clinical symptoms in combination with ECHO parameters. ECHO criteria of the diagnosis should be based on both the magnitude of the left-to-right shunt and its individual impact on the patient’s hemodynamic changes to define the optimal postnatal time for treatment.

Treatment should not harm the patient more than the disease (the open ductus) itself. Current evidence does not support prophylactic indomethacin, ibuprofen or surgical ligation. Premature closure of PDA has not been proven to affect later outcomes, and the risks of side effects of the early treatments are higher when compared to later treatment. It is important to avoid overdiagnosis and subsequent overtreatment. However, the optimal anticipation in the treatments timing is important, which mean diagnosis at the proper time and treating a hemodynamically open ductus before hemodynamic collapse. In conservative treatment, watchful waiting with fluid restriction is a good choice when ductal flow does not harm the infant but the flow pattern and clinical symptoms require therapeutic attention. Medical treatment is the primary choice, followed by surgical ligation according to clinicians’ individual choice.

A retrospective study of paracetamol (I) discovered that the incidence of PDA was apparently decreased with no adverse effects after introduction of paracetamol for treatment of pain in VLGA infants. In the present RCT, the infants were treated with a four-day course of paracetamol or placebo. We found for the first time that paracetamol has a biological effect on the early constriction of PDA in very preterm infants. Although the precise mechanism of paracetamol is unclear, it inhibits the peroxidase moiety of the prostaglandin synthase enzyme, thus decreasing the main ductal vasodilator PGE₂ (with PG₁) levels. Prostaglandin levels drop, and the DA contracts. According to present RCTs and additional studies (Dang et al., 2013; El-Mashad et al., 2017; Oncel et al., 2014; Yang, Gao, Ren, Wang, & Zhang, 2016), there is sufficient evidence to indicate that paracetamol could be a new medication for closure of PDA in premature infants. It has been shown to have the same effect as the NSAID drugs ibuprofen and indomethacin, but with fewer acute side effects on the kidneys and the gastrointestinal tract. This is because paracetamol does not cause generalised vasoconstriction as do the COX-inhibitors ibuprofen and indomethacin (Gournay et al., 2004).
The optimal time for therapeutic closure of PDA in very premature infants is controversial. Premature closure with either medication or ligation has been associated with adverse effects in several studies, although in theory it would be an attractive approach. Study II indicated that very early administration of paracetamol using the dosage effective for the treatment of pain did not result in obvious adverse effects. In ELGA infants, however, no effect on the DA was observed; these infants had neither benefits nor adverse effects. This raises some questions about whether the dose or regimen should be different in the most immature infants, those born under 28 weeks. Study II also showed that male infants responded better to paracetamol than females, but possibly because of the small sample size, this result was not statistically significant. The sample size of Study II was able to prove evidence that paracetamol has an acute effect to PDA, but it was not powered enough to show the effects in the subgroups. However, the study’s findings on efficacy and safety were promising enough to indicate further studies, including a large randomised trial.

The dose and course regimen for PDA closure are unclear, especially for the most immature infants. The effect of paracetamol might be dose dependent, and serum concentrations required for PDA closure might be higher than required for the treatment of pain and antipyretics. Paracetamol is a safe drug when used in regular doses, but there is still no evidence regarding adverse side effects, in the long term. Therefore, it cannot be recommended as a first line-therapy for PDA.

The role of prolonged left-to-right shunt and its consequences for later outcomes is controversial. There may be bias in studies comparing “standard” treatments and conservative treatment because groups may differ in origin or confounding factors (e.g., hospital differences) may make the cause-consequence analyses difficult or even impossible. Prolonged open ductus is associated with BPD, but so are the treatments (R. I. Clyman, 2013; Madan et al., 2009; Schmidt et al., 2006; Terek, Yalaz, Ulger, Koroglu, & Kultur, 2014). The possible role of PDA in BPD aetiology is unclear. The precise time postnatally when the ductal shunt changes from physiological to pathophysiological, thus causing higher morbidity and mortality for premature infants, is also controversial. The epidemiological study III showed that all therapies for PDA were associated with severe BPD. The strongest association was seen in those infants who had surgical ligation of PDA after failed medical therapy. Indomethacin has been implicated in oliguria and fluid retention, potentially predisposing premature infants to lung oedema (Schmidt et al., 2006). Surgical ligation (prophylactic, primary or secondary) for PDA has shown to associate with an elevated risk of BPD (R.
Clyman et al., 2009; R. I. Clyman, 2013). There were 112 infants in Study III who underwent direct ligation for PDA. Unfortunately, the reason for choosing direct ligation was not identifiable in the data. Most of those infants were ELGA and the association with severe IVH and ligation must be interpreted with caution, as the order of these events is unclear. Severe IVH in very preterm infants mostly occur during the first 3-4 days of life, and the risk is highest in ELGA infants (Szpecht, Szymankiewicz, Nowak, & Gadzinowski, 2016). In some cases, the diagnosis of severe IVH may be considered a contraindication to medical therapy of PDA. However, as the risk of IVH was almost five-fold higher in infants with early ligation compared to late ligation (> 7 days of life), the potential role of early ligation in the development of IVH is worth considering. Surgical closure of PDA may cause a rapid increase in cerebral perfusion. This in combination with the fragile vasculature of the germinal matrix and potential reperfusion injury is likely to predispose to bleeding. In the Study III surgical ligation was associated with risk of NEC. This finding is in accordance with that of a previous study, which found a significantly lower rate of NEC in ELGA infants treated by a conservative approach in comparison to infants treated with early ligation following indomethacin therapy (Jhaveri et al., 2010).

Although epidemiological studies III and IV were comprehensive, they have several limitations. As with all register-based studies the cause-and-effect relationships are difficult to verify and should be considered only as associations. A range of hospital-driven, genetic and acquired factors may potentially influence the outcome. Due to the variability in diagnosing hemodynamically significant PDA the diagnosis depends on both the centre and the individual clinician. Although the results confirm and extend the associations between PDA and life-threatening morbidities that have been obtained in other studies of smaller populations, further prospective follow-up studies are needed.

In conclusion, these results show that ductal treatment should always be based on a precise and comprehensive clinical (individual) evaluation of both of the risk of the large ductal shunt and possible adverse consequences of hsPDA treatments. Paracetamol may prove to be particularly suitable treatment for early closure of ductus as it additionally appears to be safe. However, more prospective trials are needed to show the optimal treatment, dosage, time, and associations of the treatments for later outcomes.
7 Conclusions

- The incidence of PDA decreased after the start of paracetamol administration in the NICU.
- IV paracetamol had a favorable effect on DA contraction.
- No acute adverse effects of paracetamol were seen.
- Paracetamol is a potentially safe and effective drug that induced closure of the DA in very preterm infants. At present, it cannot be recommended for first-line therapy in treatment of PDA in premature infants. More prospective studies are needed to determine before high-quality evidence of the dosage and the long-term side effects.
- Conservative management (watchful waiting) is a valid therapy for PDA when the open ductus does not harm the patient’s hemodynamic and organ perfusion. Because of the possible side effects of routine therapies, premature closure of the DA with currently available drugs, and in particular, routine early ligation should be avoided.
- Both medical therapy and surgical ligation associated with later risk for severe BPD.
- Direct ligation very early (before 7 days of life) is associated with severe IVH and NEC.
- PDA treatments were not associated with higher mortality in ELGA infants.
References


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Original publications


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Original publications are not included in the electronic version of the dissertation.
1467. Tikkanmäki, Marjaana (2018) Preterm birth and parental and pregnancy related factors in association with physical activity and fitness in adolescence and young adulthood


1473. Lantto, Ulla (2018) Etiology and outcome of PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome among patients operated with tonsillectomy in childhood

1474. Hintsala, Heidi (2018) Cardiovascular responses to cold exposure in untreated hypertension


Pia Härkin

CLOSURE OF PATENT DUCTUS ARTERIOSUS IN VERY PRETERM INFANTS

POTENTIAL ROLE OF PARACETAMOL AND CONSEQUENCES OF CURRENT TREATMENTS