Is Expectant Management Noninferior to Early Ibuprofen for Patent Ductus Arteriosus?

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SUMMARY

In this multicentre non-inferiority trial, 273 infants with echocardiographically confirmed PDA (diameter >1.5 mm) who were extremely preterm (<28 weeks gestational age) underwent randomization to receive either expectant management or early ibuprofen treatment. The composite primary outcome included necrotizing enterocolitis (Bell's stage IIa or higher), moderate to severe bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age. The median gestational age was 26 weeks, with a median birth weight of 845 g. A primary-outcome event occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 (63.5%) in the early-ibuprofen group (absolute risk difference, -17.2 percentage points; upper boundary of the one-sided 95% confidence interval [CI], -7.4; P<0.001 for noninferiority). Necrotizing enterocolitis occurred in 24 of 136 infants (17.6%) in the expectant-management group and in 21 of 137 (15.3%) in the early-ibuprofen group (absolute risk difference, 2.3 percentage points; two-sided 95% CI, -6.5 to 11.1); bronchopulmonary dysplasia occurred in 39 of 117 infants (33.3%) and in 57 of 112 (50.9%), respectively (absolute risk difference, -17.6 percentage points; two-sided 95% CI, -30.2 to -5.0). Death occurred in 19 of 136 infants (14.0%) and in 25 of 137 (18.2%), respectively (absolute risk difference, -4.3 percentage points; two-sided 95% CI, -13.0 to 4.4). The authors concluded that expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age.

COMMENTARIES

Evidence-based Medicine Viewpoint

Critical Appraisal

The classical presentation of hemodynamically significant (hs) patent ductus arteriosus (PDA) in extreme preterm neonates comprises of increase in pulmonary blood flow leading to pulmonary oedema, respiratory deterioration, and sometimes bronchopulmonary dysplasia (BPD). The alteration in blood flow due to hsPDA may also cause necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), and even death [1].

The incidence of PDA beyond the first 3 postnatal days exceeds 50% in infants less than 28 weeks gestation. Historical practice has led to medical or surgical therapy in 60% to 70% of such infants [2,3]. The available pharmacological modalities include cyclooxygenase inhibitors and surgical ligation for non-responders. These therapies have their own risk, and the metanalyses evaluating the outcomes of pharmacotherapy lack robustness to refute the role of expectant management [4,5].

Over the years the evidence has moved from intervention to expectant management of PDA in preterm. Observational evidence suggests that conservative management using supportive therapy alone in preterm infants with PDA may be a reasonable option with ongoing assessment and intervention if needed [6]. In a network meta-analysis that compared all pharmacological methods versus placebo or no treatment, the latter had the poorest rate of PDA closure. However, all treatment options (including placebo and no therapy) had similar outcomes of patient-centred outcomes, such as mortality, NEC, or IVH [7].

The BeNeductus trial [8] compared expectant management vs early Ibuprofen therapy for PDA in pre-term neonates <28 weeks who had echocardiographically confirmed PDA, ductal diameter >1.5 mm and left-to-right shunt detected at 24-72 hours of age. The *a priori* non-inferiority margin was an absolute risk difference of +10%. The primary outcome was a composite of NEC, moderate-to-severe BPD or death at a postmenstrual age of 36 weeks. The authors were able to achieve only 48.4% of the calculated sample size. Despite the inadequate sample size, the results showed that expectant management was non-inferior to early ibuprofen therapy vis à vis the composite outcome, and sepa-

rately BPD and death. In fact, the results suggest a significantly higher incidence of BPD in the ibuprofen group.

Conclusion

This trial adds to the growing evidence that non-pharmacological conservative treatment is effective in most preterm neonates. There is a need to find the subset of preterm who would need PDA closure. The trial throws up the interesting possibility that ibuprofen may worsen pulmonary outcomes through mechanisms that need further elucidation.

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Neonatologist's Viewpoint

Patent Ductus Arteriosus (PDA) occurs commonly among preterm infants with incidence being as high as 50-80% among extreme preterm infants (<28 weeks) [1, 2]. Closing PDA early in the course would possibly prevent PDA associated mortality and various morbidities including bronchopulmonary dysplasia (BPD), pulmonary haemorrhage, intra-ventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC). However, there is a controversy about the optimal management of PDA with recent trend shifting towards 'expectant' management.

Traditionally neonatologists have followed four different kinds of approaches for treating PDA. These are 1) Prophylactic treatment (within 24 hours of birth) 2) Pre-symptomatic/early treatment (usually 3-7 days after birth) 3) Symptomatic treatment (after 1st week of life) 4) Expectant management. All these approaches have their own pros and cons with the 'prophylactic' strategy being out at present as large proportion of infants get exposed to potential serious side effects of drug treatment, when their PDA would have been closed spontaneously. Moreover, it has not shown any significant advantage on the mortality or long-term neurodevelopmental outcome [3]. Though, the trials assessing the effectiveness of 'early treatment' versus 'expectant' management for hemodynamic significant PDA (hs PDA) did not find any significant difference in any of the morbidity or all-cause mortality however, critical analysis of these trials revealed that a significant proportion of infants (20-85%) in the 'expectant' management group received 'open-label' treatment thus contaminating the overall results [4]. Thus, there is a research gap where 'expectant' management has been compared with 'early treatment' strategy in extreme preterm infants with minimal to no contamination.

Hundscheid, et al, in this multicentric, non-inferiority trial randomized extreme preterm infants with echocardiographically confirmed PDA (>1.5 mm with left-to-right shunting) within first 72 hours of life to receive either 'expectant' management (intervention) or 'early-ibuprofen' treatment (active control). The primary outcome was the composite of definite NEC, moderate-to-severe BPD or death at 36 weeks' of postmenstrual age with a non-inferiority margin of 10% [5]. The trial was stopped prematurely due to slower-than-anticipated recruitment and could enroll only half of the expected sample size. The 'expectant' management was found to be non-inferior to 'early-ibuprofen' treatment with absolute risk difference of the composite primary outcome being -17.2% (63/136 [46.3%] in 'expectant management' group versus 87/137 [63.5%] in 'early-ibuprofen' group) with upper boundary of one-sided 95% confidence interval being -7.4%. The results were largely driven by higher incidence of BPD in 'early-ibuprofen' group than in the 'expectant' group [57/137 (50.9%) vs 39/136 (33.3%)].

Though, the results of this trial are significant however, half of the infants received diuretics and 25% received paracetamol in the 'expectant' group, thus contaminating the results. This is despite of the fact that the protocol explicitly highlighted to have avoidance of such co-interventions to

get the true difference. No information is available about the daily fluid intake. It is important to know the same as fluid restriction is one of the early intervention done in preterm infants with hs-PDA. Moreover, the results in this open-label trial are primarily driven by the difference in the incidence of BPD and excess fluid has been directly implicated in the patho-physiology of BPD. Also, there is no information about the number of infants receiving 'open-label' treatment. It is worth noting that one-third of the infant deaths (6/19) occurred beyond first 28 days of life in 'expectant' group unlike 'early-ibuprofen' group where no more deaths occurred beyond this time period. This difference may also reflect performance bias in this open-label trial with more care being given to infants in the 'expectant' group especially in first few days of life when hs-PDA is active requiring treatment.

Though the results of this trial are encouraging and reassures that the 'expectant' group is noninferior to 'early-ibuprofen' group in short-term, however, being underpowered with above-mentioned limitations, one need more evidence in this direction to change the current practice. Another similar trial named 'baby-OSCAR' addressing the similar research question has finished the enrolment and the results are awaited soon [6].

Thus, both strategies i.e., 'expectant' management and 'early/late treatment' have their own role to play however; there is a need to identify the subgroup of infants who would benefit maximum with minimal adverse events with each of these two strategies. Till we have more evidence it's appropriate to conclude what Evan's said *"It is the clinical approach that is most widely used but we do not have any evidence to support it"* [7].

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Pediatrician's Viewpoint

Patent Ductus Arteriosus (PDA) is one of the most common congenital heart defects seen in neonates. Its incidence is inversely related to the gestational age and degree of prematurity. Failure of closure of ductus is seen in 64% neonates born at 27-28 weeks of gestation at 7 days of life in 80% of those between 24-28 weeks and 90% in those born less than 24 weeks of gestation [1]. Prolonged rupture of membranes, sepsis, respiratory distress syndrome, are some risk factors reported with increased incidence of PDA. Use of antenatal steroids is reported to be beneficial specially when administered at least 24 hours before delivery, thereby reducing the incidence of PDA [2].

Management of PDA in preterm neonates has been a topic of debate with a shift in management strategy in the last 30 years. With increasing use of antenatal steroids, exogenous surfactant and advances in ventilation strategy has shifted management strategy from aggressive early closure to Wait and Watch policy [3]. Numerous studies are available documenting an association between necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) and PDA. Prolonged shunt exposure and high left to right shunt volume across the ductus are some factors suggested [4]. However, there are multiple randomized controlled trials (RCT) that have failed to show any improvement in these morbidities even after early closure of PDA and prophylactic surgical ligation no longer recommended due to reported associated significant morbidities [5,6]. Even in this study, expectant management of PDA is extremely premature infants was found to be no inferior to early ibuprofen therapy with respect to NEC, BPD or death at 36 weeks' postmenstrual age. Similar findings have been reported in the past in meta-analysis and placebo controlled RCT [7,8]. Therefore, management of PDA continues to be a challenge with pharmacogenetics seeming to be the next management strategy in premature infants with the ongoing debate as to who needs intervention minimising the morbidity and mortality.

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