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Editorial

Management of persistent ductus arteriosus in very premature neonates. Results of the French TRIOCAPI trial, perspectives for clinicians, and subsequent studies on this topic

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Over the past four decades, the management of persistent ductus arteriosus (PDA) in newborns has remained a hotly debated topic and there is currently no consensus on who, when, and how to treat. While some authors argue that a PDA is an innocent bystander, making treatment unnecessary and potentially dangerous [1], others are concerned about the potential harmful effects of a PDA, which include pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), hypotension, intraventricular hemorrhage (IVH), necrotizing enterocolitis, and mortality [2]. Current PDA treatment strategies vary from an early pharmacologic approach to a conservative approach, with specific criteria for late pharmacologic treatment.

Routine prophylactic treatment with indomethacin or ibuprofen, administered in the first hours of life, has been shown to have short-term benefits, such as reductions in the incidences of symptomatic PDA, need for PDA ligation, and early pulmonary hemorrhage. A decrease in the incidence of serious IVH among infants treated with prophylactic indomethacin has also been found in randomized controlled trials (RCTs) performed prior to 2000. However, prophylactic treatment unnecessarily exposes 30–50% of premature babies, in whom the ductus is likely to close spontaneously within the first week, to the potential adverse effects of cyclooxygenase inhibitors and does not improve survival without neurosensory impairment [3].

In order to decrease the number of unnecessarily treated infants, an early, targeted prophylactic PDA treatment approach has been proposed, where echocardiographic examinations are performed during the first day and early routine pharmacologic treatment is given only to infants with large PDAs. Theoretically, such an approach would have the best risk–benefit ratio. The DETECT (Ductal Echocardiographic Targeting and Early Closure Trial) trial, performed in three Australian tertiary neonatal intensive care units (NICU), demonstrated that it was indeed feasible to identify a subgroup of infants with a large PDA among infants born before 29 weeks' gestation in the first 12 h after birth. The treatment of these patients with indomethacin was associated with significant reductions in early pulmonary hemorrhage and in the need for subsequent PDA treatment. The trial also showed that early echocardiography can detect infants with a small PDA who are at low risk of pulmonary hemorrhage and have an 80% rate of spontaneous PDA closure [4].

Several factors prompted the need for a TRIOCAPI (*T*argeted by Echocardiographic *T*reatment *o*f the Ductus *A*rteriosus in *P*reterm Infants by *I*buprofen) trial. First, the Australian trial examined indomethacin, not ibuprofen that is the drug available for PDA treatment in French NICUs. Second, the DETECT trial had to be stopped before study completion due to the removal of intravenous indomethacin from the Australian market. And finally, the primary outcome of the Australian trial was a short-term outcome (death and/or abnormal cranial ultrasound at nursery discharge); no information was gathered about survival without cerebral palsy (CP) at 24 months of corrected age. In the TRIOCAPI trial 337 preterm infants with < 28 weeks' gestation were recruited between 2012 and 2017, from 11 French tertiary-care NICUs [5]. Among them, 228 (68%) infants had a large PDA and were randomized to receive ibuprofen or placebo (114 in each group). The trial confirmed the results of the DETECT trial, i.e., early targeted treatment of a large PDA reduced pulmonary hemorrhage and later need for PDA rescue treatment. Early ibuprofen treatment increased the rate of DA closure at day 3; however, it did not reduce the risk of high-grade IVH, suggesting that DA size is not the primary determinant of cerebral hemorrhage in these patients [6]. Although observational studies have found that early PDA screening reduces in-hospital mortality among extremely preterm infants [7], infants receiving early ibuprofen treatment in the TRIOCAPI trial had the same incidence of brain injury-free survival at 2 years corrected age as those receiving placebo. The rate of CP was similar in both groups and was consistent with current prevalence rates [8]. It is worth mentioning that among the secondary outcomes there was a trend toward better neurodevelopmental scores, assessed with Ages and Stages Questionnaire (ASQ) at 2 years corrected age, in infants treated with ibuprofen. This finding warrants additional investigation.

Although the TRIOCAPI trial demonstrated that there was little benefit in routine PDA treatment during the first day, even among those with a large PDA, it cannot address the question of whether a large PDA should be closed or allowed to persist throughout the neonatal period. Both the high rate of spontaneous constriction (39% within 2 days) and the high rate of early open-label PDA treatment (61% of placebo infants received rescue back-up ibuprofen by 3–4 days) insured that by 14 days 70% of infants in both study groups had a closed or closing ductus flow pattern. Both issues have limited the

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interpretation of many other double-blind RCTs. The use of early back-up treatment suggests that study investigators still may be reluctant not to treat a widely patent DA. On the other hand, the high rate of spontaneous constriction suggests that early measurement of PDA size may be a poor indicator of its subsequent hemodynamic significance and better predictors need to be found.

Fortunately, more information should be forthcoming from other RCTs (UK [EudraCT 2013-005336-23], Belgium/Netherlands [NCT02884219], Ukraine [NCT03860428], and USA [NCT03456336]) comparing ibuprofen with placebo or expectant management. Pending the results of these RCTs, PDA management should be tailored to each infant based on individual characteristics, risk factors, and an understanding of the risks and limited benefits of PDA treatment. Gestational age of <26 weeks and lack of antenatal glucocorticoids should be considered in the decision, since they have been associated with low rates of spontaneous closure [9]. Use of a PDA severity score, like the one described by McNamara and Seghal (which combines clinical, laboratory, and echocardiographic criteria) may help in identifying potential candidates for treatment and comparing outcomes among different institutions [10].

Decisions about PDA treatment will also need to consider the patient's evolving respiratory and hemodynamic status as well as the duration of ductal patency, since these factors appear to alter the impact of a PDA on other neonatal morbidities. In a secondary analysis of the TRIOCAPI trial, an important interaction was found between the duration of ductus patency and the duration of invasive ventilation on the incidence of BPD-any grade, as defined by the room air challenge test performed at 36 weeks' postmenstrual age [11]. In multivariable regression analyses, infants with prolonged (≥14 days) exposure to a moderate-to-large PDA shunt had an increased incidence of both BPD (odds ratio [OR], 95% confidence interval [CI] = 3.00 [1.58–5.71]) and the combined outcome BPD/death (OR, 95% CI = 2.41 [1.47–3.95]) – but only when the infants also required intubation for longer than 10 days [12]. Infants who received less ventilatory support (intubation for less than10 days) had the same incidence of BPD and BPD/death whether the ductus closed shortly after birth or whether it persisted as a moderate-to-large shunt for several weeks. Similar findings have been reported from the PDA-TOLERATE trial [13]. These findings suggest that if a clinician's primary reason for wanting to treat a PDA is "to decrease the incidence of BPD," then PDA treatment may be unnecessary if infants require only short durations of intubation (<10 days). In infants who require short durations of intubation, the presence or absence of a PDA does not seem to alter the incidence of BPD.

These results from the TRIOCAPI trial demonstrate that a coordinated approach among different treatment modalities may improve neonatal outcomes. An increased emphasis on noninvasive ventilation in the delivery room, as well as in the intensive care nursery, is likely to diminish the impact of the PDA on respiratory outcomes and should be part of this strategy. Prior studies have demonstrated the utility of such bundles of care for other severe morbidities in very preterm infants [14].

The TRIOCAPI trial also identified several concerns that should be addressed in future studies. There was a trend for high-grade IVH and gastrointestinal perforations to be increased in patients allocated to the early ibuprofen treatment group, with *p* values, respectively, equal to 0.20 and 0.11. This highlights the need for finding pharmacologic agents with safer risk profiles. Acetaminophen, with its presumed superior safety profile, may represent an alternative treatment option, but data about its pharmacologic profile, efficacy, and safety are limited in extremely preterm infants [15]. Fortunately, more than 20 trials examining acetaminophen are currently underway. Among these, TREOCAPA (NCT04459117) assesses the effects of prophylactic PDA treatment with acetaminophen. The trial is a phase II/III trial and involves 60 NICUs in 17 European countries (including 13 NICUs in France). The primary objective is to demonstrate, among infants born < 29 weeks' gestation, a 10% increase in survival without severe morbidity at 36 weeks in infants treated with prophylactic acetaminophen. A positive result could change current treatment algorithms by altering the risk–benefit ratio of PDA treatment, even if it would not address all the residual concerns about who or when to treat.

Declaration of Competing Interest

None.

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