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The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants

William E. Benitz*, Shazia Bhombal

Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, CA, USA

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A B S T R A C T

Over the last four decades, non-steroidal anti-inflammatory drugs have been widely used to induce closure of the patent ductus arteriosus (PDA) in preterm infants. Evidence to support this practice is lacking, despite performance of >50 randomized trials. The credibility of those trials may have been compromised by high rates of open treatment in controls, era of study prior to advent of modern practices, or inclusion of insufficient numbers of very immature infants. Meta-analyses show little impact of those factors on main conclusions. Essentially all trials reporting important long-term outcomes (other than mortality) initiated treatment within five days after birth, so no evidence regarding later treatment is available. Accruing clinical experience suggests that long-term outcomes are not compromised, and may be improved, with non-interventional management strategies. Future studies to identify preterm infants at greatest risk of potential harm from a persistent PDA, particularly after the second postnatal week, are urgently needed.

1. Historical perspective

Only four years after Burnard's seminal report in 1959 that persistence of the murmur of a patent ductus arteriosus (PDA) in preterm infants is associated with more severe signs of respiratory distress [1], Decanq reported ligation of the ductus in an eight-week-old infant born at 32 weeks gestation, who weighed 1417 g at the time of surgery [2]. Early reports of successful ductal ligation in preterm infants were followed by several larger case series that suggested clinical improvement following ligation in sick preterm infants [3]. As this technical capability developed, it became apparent that PDA in infants with respiratory distress syndrome was linked to bronchopulmonary dysplasia (BPD), prolonged ventilation, mortality, and worsening pulmonary disease [4]. Because of these associations, by the mid-1970s there was an emerging consensus that surgical intervention was strongly indicated in preterm infants with persistent patent ductus associated with congestive heart failure and respiratory insufficiency.

An apparently serendipitous observation of ductal constriction in an infant with ductus-dependent pulmonary blood flow in response to indomethacin [5], supported by a growing understanding of the role of prostaglandin in maintaining ductal patency, led to the suggestion that indomethacin might provide a means for inducing ductal closure in selected instances of prolonged patency. In simultaneous reports in the *New England Journal of Medicine* in 1976, these observations were translated into clinical application [6,7]. In those seminal reports, ductal closure within 30 h occurred in 19 of the 21 infants treated with indomethacin. In an editorial in the same issue, Nadas strongly advocated for surgical closure in the first week after birth, and urged caution in adoption of pharmacologic methods for closing the ductus until controlled trials had been completed [8]. Nadas then led efforts to organize the landmark National Collaborative Study on Patent Ductus Arteriosus in Preterm Infants [9]. Because the belief that closure of the PDA was imperative had already become so ingrained in the neonatology and pediatric cardiology cultures, that study was designed to ensure that ductal closure was achieved in all subjects [9]. Open treatment of control subjects to close the PDA has been a widespread, but not quite pervasive, problem in subsequent controlled trials of PDA closure. The underlying belief in the necessity of treatment remains strong.

Against this background, some authors questioned the need for interventions to control ductal patency. As early as 1963, Powell noted spontaneous closure of persistent PDA in five of six preterm infants [10]. In 1966, Auld reported seven infants with respiratory

* Corresponding author. Division of Neonatal and Developmental Medicine, 750 Welch Road, Suite 315, Palo Alto, CA 94306, USA.
E-mail address: benitzwe@stanford.edu (W.E. Benitz).

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distress syndrome and PDA, including two with severe congestive failure, who recovered with medical management alone [11]. Over the next four decades, other voices continued to note the lack of evidence to support a policy of intervention to close PDA before or soon after development of signs of significant shunt flow [4,12,13]. In this review, we will present the state of the evidence related to long-term benefits of treatments to close PDA, with a focus on the role of non-steroidal anti-inflammatory drugs (NSAIDs).

2. Evidence for benefit from treatment

Indomethacin and ibuprofen, non-selective cyclo-oxygenase 2 inhibitors, mediate ductal closure through inhibition of synthesis of prostaglandin E_2, which prolongs ductal patency through vasodilation [14]. Both have been extensively studied in the preterm population. Numerous studies have confirmed those early observations that NSAID treatment is effective in inducing closure of the ductus arteriosus in preterm infants. The pooled odds ratio for persistent ductal patency after NSAID treatment for any indication is 0.25 [95% confidence interval (CI): 0.22–0.28] (Fig. 1). A few small case series and examination of data from early clinical trials [15] suggested that the efficacy of NSAID treatment decreases

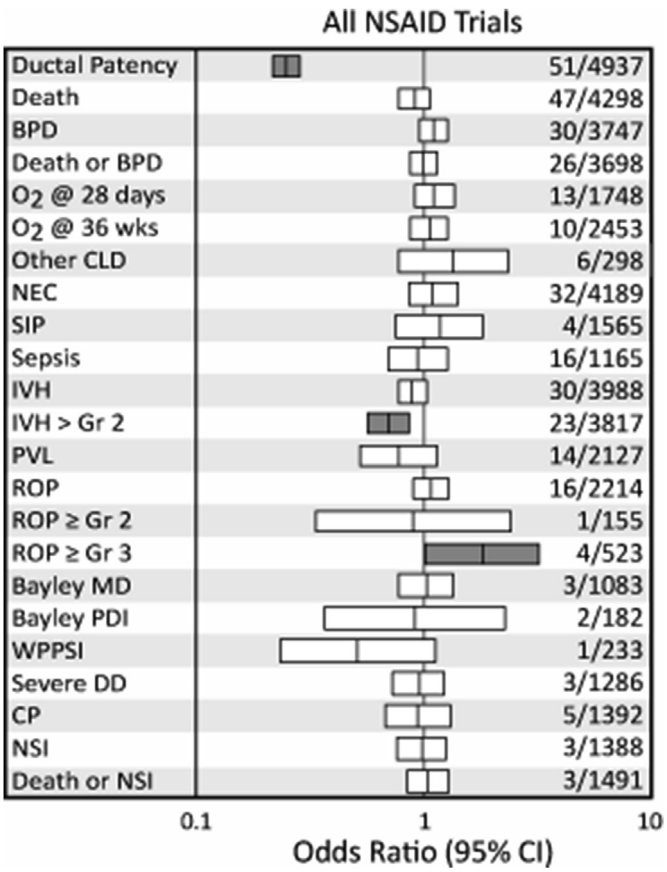

Fig. 1. Pooled results of randomized controlled trials of NSAID therapy for persistent patent ductus arteriosus in preterm infants. Bars represent 95% confidence limits and the line at the midpoint of each bar denotes the point estimate of the pooled odds ratio. Bars for odds ratio significantly different from 1 are grey (two-tailed $P < 0.05$). The numbers of trials (N) and subjects (n) for each outcome are shown at the right (N/n). BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; MDI, Mental Development Index; PDI, Psychomotor Development Index; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; DD, developmental delay; CP, cerebral palsy; NSI, neurosensory impairment.

significantly after a postnatal age of approximately two weeks. This relationship may be mediated by loss of sensitivity of the ductus to NSAID exposure after a postmenstrual age of about 34 weeks [16]. Achievement of ductal closure is more likely to follow a first course of indomethacin than second or third courses (63% vs 27%, $P = 0.001$) [17]. There do not appear to be significant differences among the available agents (indomethacin, ibuprofen, acetaminophen) with respect to likelihood of achieving ductal closure or avoiding surgical ligation [18,19]. The critical question, however, is not when to treat infants with PDA with NSAIDs or with which drug, but whether the effect of NSAIDs on ductal patency results in better long-term outcomes in treated infants.

Between 1980 and 2016, this question has been addressed in 51 randomized controlled trials of NSAID treatments in preterm infants, which enrolled 4937 infants [4,20–22]. Most trials (41) used indomethacin, nine used ibuprofen, and one used acetaminophen. Treatment was given as prophylaxis in 29 studies, for asymptomatic PDA in six, and for symptomatic PDA in 16. Despite consistent efficacy in closing the PDA, these studies have failed to detect either adverse or beneficial effects of treatment, with very few exceptions. In those exceptional instances, the observed differences have only rarely been reproducible. Meta-analyses of those studies or various subgroups of them have consistently failed to identify beneficial effects of inducing closure of the PDA with NSAID therapy, whether strict [18,19,23–26] or permissive [4] criteria for study inclusion were used. Results of a meta-analysis including all 51 NSAID trials (performed as previously reported [4] but for this distinct collection of trials) are shown in Fig. 1. As in prior analyses, treatment was very effective in achieving ductal closure, the rate of intraventricular hemorrhage of severity higher than grade 2 was significantly lower, and the rate of retinopathy of prematurity at grade 3 or higher was significantly increased. There were no apparent effects on other outcomes, including neurodevelopmental impairment (the 95% confidence intervals for the odds ratios include 1). The confidence intervals for most outcomes are narrow, indicating that these conclusions are unlikely to be altered by additional trials, unless the observed effect and sample size are very large. This body of evidence provides no support for the hypothesis that NSAID treatment to close the PDA in preterm infants improves long-term outcomes.

3. Adverse effects of treatment

Despite the widespread belief that ductal closure leads to improvement in respiratory dysfunction, evidence from randomized trials suggests otherwise. A small, early trial found that indomethacin-treated infants weaned from both ventilator support and supplemental oxygen sooner than placebo-treated controls, but (despite randomization) the indomethacin-treated infants were significantly larger and more mature [27]. Compared to placebo-treated infants, those randomized to early treatment with indomethacin achieved significantly longer duration of positive pressure ventilation [28]. Infants <1750 g randomized to treatment with indomethacin beginning at 12 h of age required more oxygen and had larger alveolar–arterial oxygen gradients than those administered placebo [29]. Infants <28 weeks gestation randomized to indomethacin treatment at age 3 days required more supplemental oxygen and higher mean airway pressures from day 3 through day 8 than those treated at age 7 days of age [30]. In the Trial of Indomethacin Prophylaxis in Preterms, extremely low birth weight (<1000 g) infants who received indomethacin prophylaxis had higher F_IO_2 requirements on postnatal days 3–7 (and possibly longer) compared to infants who received placebo [31]. Other randomized trials that reported effects of NSAID treatment on days of ventilation or oxygen use or other indicators of pulmonary

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