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SPECIAL ISSUE ARTICLE

WILEY Congenital Heart Disease

Pharmacotherapy for patent ductus arteriosus closure

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Abstract

Even though up to 60% of premature infants less than 28 weeks gestation develop persistent patent ductus arteriosus (PDA), there remains controversy regarding if, when, and how to close the PDA. Failure to close the PDA has been associated with significant morbidity but no cause-and-effect has been proven for short-term or long-term outcomes in modern times. Surgical closure has the advantage of eliminating the PDA, but short-term complications and long-term adverse outcomes are worrisome. Intravenous indomethacin has been the "gold standard" for pharmacologic treatment over the past 40 years with high closure rates and decreased incidence of severe intraventricular hemorrhage (IVH) and pulmonary hemorrhage with early treatment but without improvement in long-term outcomes and with risk of renal toxicity. Intravenous ibuprofen has less vasoconstrictive toxicity than indomethacin with comparable closure rates but without improvement in IVH and with hyperbilirubinemia risks. Earlier this decade, acetaminophen (paracetamol) was discovered to effectively close the PDA with good short-term safety profile. Although promising, acetaminophen treatment requires further studies regarding long-term safety as well as ideal dosing and route of administration.

KEYWORDS

acetaminophen (paracetamol), cyclooxygenase (COX) inhibitors, ibuprofen, indomethacin, patent ductus arteriosus, peroxidase (POX) inhibitor

1 | INTRODUCTION

During fetal life, approximately 90% of right ventricular output is diverted away from the pulmonary circulation and toward the placenta. After birth the ductus arteriosus (DA) is functionally closed at 72 hours in most term infants but often remains persistently open in small premature babies[1] due to several factors including increased sensitivity to the vasodilatory effects of prostaglandins,[2] decreased immature lung metabolism of prostaglandins,[3] decreased DA wall tone, and increased prostaglandin receptors in the thin intima of the DA wall.[4] As pulmonary vascular resistance falls and systemic vascular resistance increases, left-to-right shunting often develops which can lead to worsening pulmonary function and systemic circulatory steal. If the PDA becomes hemodynamically significant (hsPDA) based on clinical and echocardiographic evidence, studies have shown an association with an increase in morbidity[5] although a causative link to PDA has not be proven.[6] The decision to treat requires close evaluation of the benefits and risks of the particular method of closure. Because of the short-term complications and increased long-term morbidities including retinopathy of prematurity, chronic lung disease (CLD), and neurodevelopmental impairment, benefits of surgical ligation may not outweigh the risks.[7,8] Thus, pharmacotherapy with prostaglandin inhibitors is usually the initial approach to PDA closure.

2 | HISTORY AND COST OF PDA PHARMACOTHERAPY

In 1976, Friedman and Heymann published separate data regarding the successful closure of PDA with oral and rectal indomethacin.[9,10] In 1995, intravenous ibuprofen was introduced as an effective alternative to indomethacin with less cerebrovascular constriction.[11] Both of these medications interfere with the conversion of

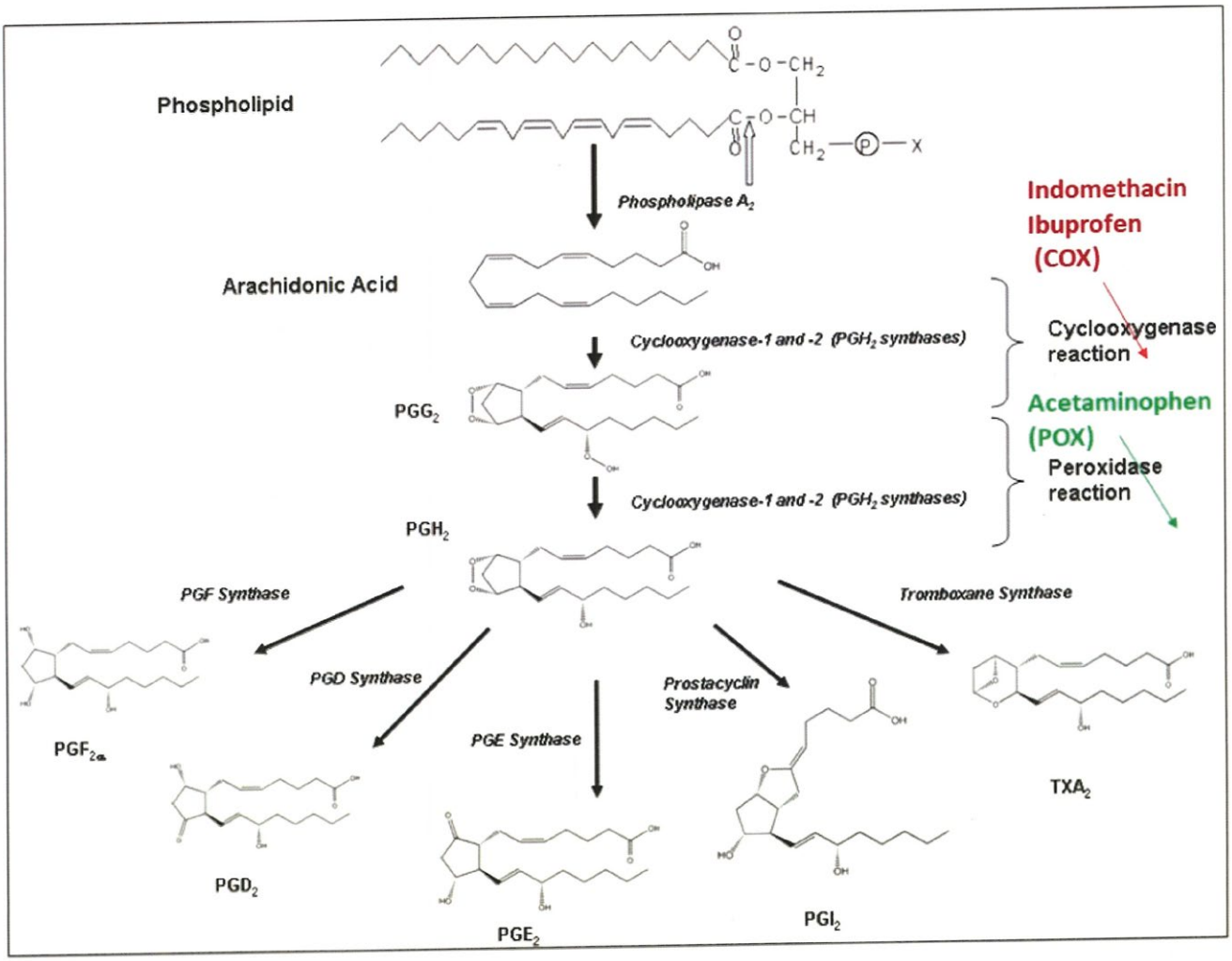

FIGURE 1 Conversion of arachidonic acid to prostaglandins via prostaglandin synthetase (cyclooxygenase and perioxidase reactions)

arachidonic acid to prostaglandins by blocking the first moiety of the prostaglandin synthase enzyme reaction, the cyclooxygenase (COX) reaction, and are thus called COX inhibitors (Figure 1). Hammerman and associates quite serendipitously discovered that oral paracetamol (acetaminophen) was successful in closing a hsPDA in a 26-week gestational baby who had failed ibuprofen therapy.[12] Although the precise mechanism is not completely understood, paracetamol appears to inhibit prostaglandin synthase activity by blocking the second reaction of the enzyme, the peroxidase (POX) component, and is thus called a POX inhibitor (Figure 1).

In our hospital, the net cost per course of intravenous acetaminophen ($540/course) is approximately one third that of the 2 COX inhibitors ($1425 and $1460 for an intravenous indomethacin and generic ibuprofen course, respectively).

3 | COX INHIBITORS

Indomethacin has been the gold standard for PDA closure for over 40 years with a closure rate of 70% or greater.[13] The timing options for indomethacin treatment are the following: prophylaxis (within 24 hours of birth), early symptomatic (1-3 days of life) and late symptomatic (7-10 days of life). The advantages of prophylactic treatment are significant decreases in severe intraventricular hemorrhage (IVH), hsPDA, pulmonary hemorrhage, and surgical ligation.[14] Because of the lack of improvement in neurodevelopment at 18 months corrected age and in CLD incidence[14] as well as the unnecessary treatment of a significant number of babies who will spontaneously close,[15] prophylactic treatment has fallen from favor. Early symptomatic treatment with indomethacin in the modern era has not shown pulmonary benefits over late symptomatic treatment.[16] One of the significant adverse effects of indomethacin therapy is the decrease in renal, mesenteric and cerebral perfusion with bolus administration which can be somewhat obviated by 36-hour continuous infusion.[17,18] Several studies have suggested that indomethacin is a more selective COX-1 inhibitor than ibuprofen causing more renal dysfunction.[19] Also, prolonged courses of indomethacin have been associated with increased incidence of necrotizing enterocolitis.[20]

Intravenous ibuprofen is as efficacious as indomethacin in closing the PDA with less renal toxicity and less systemic

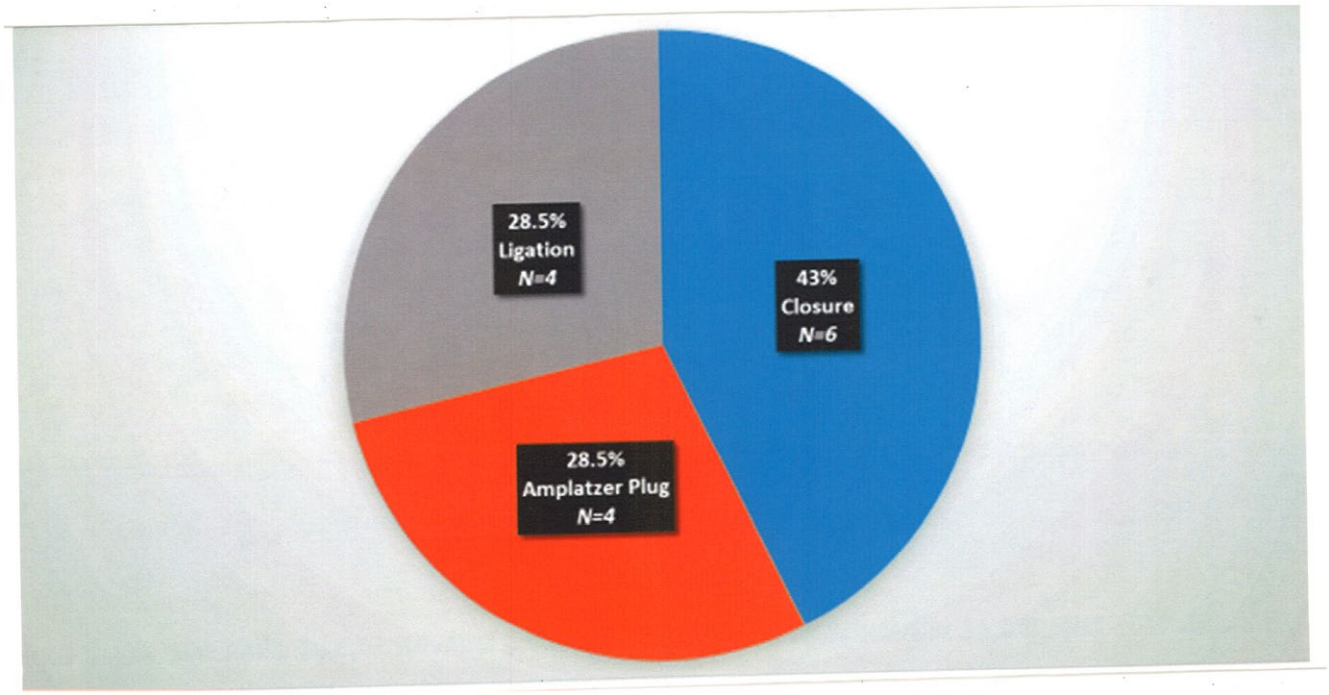

FIGURE 2 Preinvasive PDA closure with 3-day acetaminophen treatment in 14 patients (unpublished data)

vasoconstriction.[21-23] But there is a concern for bilirubin displacement due to the 99% protein binding of the medication[24] as well as increase incidence of hyperbilirubinemia, possibly due to ibuprofen's effect on glucuronidation.[24-26] Oral ibuprofen is an option but its high osmolarity in the presence of ductal mesenteric steal is concerning.[27]

4 | POX INHIBITOR

Acetaminophen (paracetamol) is promising as an alternative drug for PDA closure. It appears to inhibit the peroxidase component of prostaglandin synthase (Figure 1), even under conditions where COX inhibition is less active due to peroxidase being activated at 10-fold lower peroxide concentrations than is cyclooxygenase.[12] Other advantages are its wide availability, low cost, and low-risk hepatotoxicity in prematures due to an immature cytochrome p450 enzyme system.[28] It has been shown to be efficacious with both oral and intravenous routes of administration although the oral preparation is hyperosmolar and should be used with caution if the patient is NPO or on low-volume feedings. Liver enzymes should be checked before and after treatment. To date, there have been four large randomized control trials (RCTs) comparing acetaminophen to ibuprofen and/or indomethacin. All four trials revealed rates of closure to be comparable in all three drugs without serious short-term side effects with acetaminophen.[29-32] A meta-analysis of two RCTs and 14 uncontrolled studies revealed pooled closure rates of 49% and 76% after 3 and 6 days of treatment, respectively; good short-term safety profile; efficacy and safety comparable to ibuprofen; oral administration with more steady plasma levels than intravenous administration; and best efficacy ≥28 weeks of gestation and <7 days old.[33] One retrospective study of "late medical therapy" with preligation paracetamol at a median age of 27 days (16-39 days) revealed an immediate PDA closure rate of 25%, immediate constriction with delayed closure of 64%, and 11% with no response who were subsequently ligated.[34] Fourteen VLBW babies with median age 28.5 days (4-41 days) who were admitted between 2013 and 2015 to our regional Level IV NICU were treated with a 3-day course of acetaminophen prior to ligation or transcatheter closure. These babies were candidates for invasive closure of their PDA due to gastrointestinal contraindication to COX inhibitors or failed prior COX inhibitor treatment. Six patients (43%) responded with PDA closure, and invasive procedure was not needed. Four patients (28.5%) went on to surgical ligation and four (28.5%) to transcatheter closure (Figure 2).

Even though the short-term safety profile for acetaminophen looks good, the only long-term data to date comes from the Turkish RCT comparing oral paracetamol to oral ibuprofen. This follow-up study found no significant difference in neurodevelopment between the two groups at 18-24 months corrected age.[35]

5 | CONCLUSION

The COX inhibitors indomethacin and ibuprofen continue to be first-line pharmacotherapy for PDA closure even though they are associated with significant adverse effects. Acetaminophen appears to be a promising alternative with comparable efficacy and good short-term safety profile. Before acetaminophen can be recommended as first-line treatment, additional well-defined studies are needed for

timing of the first dose optimal dosing and duration, and route of administration as well as short- and long-term safety profiles.

AUTHOR CONTRIBUTION

Dr. Ferguson collected the data which was presented to the International PDA Symposium on 18 May 2018 and prepared the manuscript. Dr. Ajay Talati has reviewed the manuscript.

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