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Review Article

# Closure of the patent ductus arteriosus with ibuprofen and other non-steroidal anti-inflammatory medications in neonates

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**Abstract.** Pharmacological closure of patent ductus arteriosus in pre-term infants with indomethacin has been applied since the late 1970s. However, because of complications, a search for a safer and efficacious alternative continues. In this review, we look at the available evidence in the literature for and against closure of the patent ductus arteriosus with non-steroidal anti-inflammatory medications, and we present the results of our own pilot study looking at the safety and efficacy of orally administered ibuprofen on premature infants with clinically significant patent ductus arteriosus.

Key words: Patent ductus arteriosus, ibuprofen, premature neonates

## 1. Introduction

In premature babies who are very low birth weight (VLBW weight less than 1500 g) and extremely low birth weight (ELBW weight less than 1000 g), the incidence and complications arising from a persistently patent ductus arteriosus (PDA) are high. Complications can be said to arise because of two basic conditions: volume overload and the 'steal' phenomenon, especially in diastole.

Depending on the size of the shunt through the PDA, volume overloading usually results in congestive cardiac failure and increased interstitial oedema, eventually leading to respiratory distress, respiratory failure and apnoea. This can prolong ventilation in premature neonates, increasing the risk of chronic lung disease of prematurity (BPD), nosocomial infections because of prolonged ventilation and mortality.

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The steal phenomenon with diastolic run off into the lungs via the PDA, and hence lower diastolic pressure can result in perturbations in blood flow in the splanchnic and renal vessels possibly leading to necrotizing enterocolitis (NEC), bowel perforation, and worsening of renal impairment ( 1-3).

This 'steal' phenomenon had also been associated with the increased risk of intracranial haemorrhage (ICH) in premature neonates (3, 6).

### *1. 1. The controversies regarding PDA and methods of treatment*

In a recent editorial, Clyman and Chrome (4), citing meta-analyses, had questioned these occurrences as probably being co-morbidities of the premature child rather than being caused by the PDA because early closure of a PDA did not decrease the incidence of these morbidities (specifically NEC). This was also the opinion of Mehta et al, (5) as data on closure of the PDA (as of 2003) did not show any significant improvement as to the outcome of mortality, NEC, BPD or retinopathy of prematurity. Nonetheless, they concluded that medical closure of the PDA was still beneficial for the premature child with a haemodynamically significant PDA (hsPDA) decreasing the risk of congestive heart failure, pulmonary hypertension and death (4, 5).

This contradicts a previous publication where Clyman had a different view, implying that closure of the PDA in premature neonates actually improved survival and morbidity, whether surgical or medical (1). In effect the differences of view and the metaanalyses of the two time periods, depended mainly on two large multicentre trials of differing times, the earlier Ment trial (1994) versus the trial of indomethacin prophylaxis in preterms (2001, TIPP).

The Ment trial upheld the confirmed benefits found in smaller earlier trials that prophylactic closure of the PDA reduced the incidence of severe grades of ICH, symptomatic PDA and PDA ligation. The TIPP trial, which examined 1202 premature infants with birth weight of less than 1000 g, was specifically designed to evaluate the long term effects of prophylactic administration of indomethacin on survival without neurosensory impairment, with secondary goals of incidence of PDA, pulmonary haemorrhage, BPD, NEC, intracranial abnormalities and retinopathy of prematurity. While TIPP confirmed that prophylactic usage of indomethacin led to a decline in the incidence of PDA, PDA ligation, ICH (Grade 3 and 4) and pulmonary haemorrhage, it found no decrease in its other objectives (7, 8).

There were some inferences of the TIPP trial that require mention: one, this study was designed to detect a $\geq$20% change for the study parameters. This difference may actually be less given the population examined and the advances in clinical care over the years; this was also alluded to by Clymann and colleagues (9) after examining the National Institute of Child Health and Development's Neonatal Research Network Registry. The other assumption not mentioned in these studies had been the influence of indomethacin in the subgroup of patients, whose PDA would close spontaneously even without the need for pharmacological or surgical intervention, i.e. those who did not require intervention. This sub-group could actually affect the results of the trials, as indomethacin might have untoward side effects on these babies whose PDA shut spontaneously, as alluded to by Schmidt et al (8). Indomethacin use in premature neonates whose PDA spontaneously closed had increased their propensity to BPD compared to those on placebo, while further study is required, the effect of indomethacin on the premature lung may be deleterious, probably explaining why prophylactic use of indomethacin was not effective in reducing the incidence of BPD. While prophylactic use may not be appropriate, early treatment of symptomatic extremely low birth weight (ELBW) babies with PDA could show benefit. On the balance of evidence, closure of the hsPDA decreases the risk of serious grade 3 and 4 intracranial haemorrhage (4), death and cardiac failure at least, as was with the western Australian experience that took a conservative approach to management of the PDA in the preterm infant (3).

### *1. 2. Indomethacin for PDA closure and the controversies*

Surgical, and then pharmacological closure of the hsPDA with non-steroidal anti-inflammatory drug (NSAID) has been shown to be beneficial to the reduction in morbidity and mortality of premature neonates. Indomethacin, a NSAID, has been and continues to be used to aid in the closure of PDA associated with prematurity since the late 1970s. (1,2,4) Both oral and IV indomethacin has been employed in the process with good success.

Indomethacin facilitates closure of the PDA by two means: it blocks the formation of prostagladins, necessary in maintaining the PDA, and it increases the thickness of the avascular zone by causing the contraction of the circumferential and longitudinal muscles of the PDA resulting in constriction, decreasing blood flow in the vaso vasorum leading to vessel wall hypoxia with release of vascular endothelial cell growth factor.

Vascular endothelial growth factor eventually stimulates ingrowth of the neointima resulting in narrowing of the lumen of the PDA (5). However, the side effects from indomethacin are also not uncommon and range from hyponatraemia, worsening of NEC, gut perforation unrelated to NEC (2), gastrointestinal haemorrhage, transient or permanent renal impairment and transient platelet dysfunction (4,5). Although the incidence of NEC in indomethacin treated infants was not different from those on placebo, there had been trials suggesting that the effect of indomethacin increased the mortality outcome in those who were given indomethacin and had NEC, with increased bowel perforation especially those whose mothers received steroids because of preterm labour (4, 10-12).

Surgical closure of the PDA in premature neonates has its own morbidities including the pain of thoracotomy and spreading of the ribs possibly leading to prolonged ventilator dependance, infections, chylothoraces, pneumothoraces, vocal cord paresis, atelectasis and pulmonary haemorrhage from left lung compression during ligation (4,6). Among infants

treated by surgical ligation, recent evidence seems to indicate a higher incidence of BPD (6) and perhaps neurodevelopmental deficits in survivors (7). However, as with all recent comparisons of surgery versus medications, the population was heavily biased towards a preselected group of poorer outcome premature neonates having failed at least 2 courses of indomethacin or having indications precluding its use–as in intracranial haemorrhage. Surgery guarantees success of closure in almost all cases but because of the complications, it is the practice in most units to reserve surgical ligation for cases with failure of medical therapies.

*1. 3. Role of ibuprofen*

In a letter to the editor by Patel et al (13) in 1995, IV ibuprofen was proposed to be an effective alternative to indomethacin in the closure of PDA in premature neonates. This was followed by the phase 1 trial of Varivagou et al (14) in 1996 showing that IV ibuprofen could be used prophylactically to reduce the incidence of PDAs safely.

Double blind randomised multicentre controlled trials by Van Overmeire et al (15) in 1997, and in 2000 (16), revealed IV ibuprofen to be as efficacious as IV indomethacin in the closure of PDAs in premature neonates, but with less adverse events as regards to oliguria and raised serum creatinine, without any significant difference between the other variables such as NEC, BPD, mortality or ICH. However, there were a few instances of pulmonary hypertension requiring treatment in the IV ibuprofen group–more so with the tris- hydroxymethyl-aminomethane (THAM) formulation than the lysine formulation (3 in one study vs 1 case report respectively) (17). Contrast this with indomethacin usage which has no recorded cases requiring nitric oxide. However, as mentioned earlier, indomethacin usage predisposes the premature neonate to the need of supplemental oxygen, usually prolonging ventilation (8).

Due to the costs involved and the difficulty of obtaining IV medications in the developing world, oral medications are still used in a number of neonatal units to shut the PDA. Oral indomethacin had been used previously in our unit as well as others (2). A Hong Kong group led by Ng et al (18) compared oral sulindac versus IV indomethacin, with sulindac proving to have similar efficacy, but unacceptable mortality from gastrointestinal haemorrhage. Oral ibuprofen was used in our unit from 1999, after a trial study was performed and this was presented at the 23rd Malaysian Paediatric Association congress in 2000. The objectives of our pilot study were to ascertain the efficacy and safety of oral ibuprofen in the closure of the PDA in premature neonates who had symptomatic PDA (Phase 1 trial).

In this trial, all pre-term infants of 34 weeks gestation or less, admitted to our neonatal intensive care unit over a period of a year were considered for the study.

Only those with clinical signs – tachycardia as defined by a heart rate of more than 170 beats per minute, bounding pulses, hepatomegaly, tachypnoea with or without oxygen supplementation (not necessarily ventilated), and who were confirmed to have a PDA by 2D echo and colour Doppler were admitted into the study.

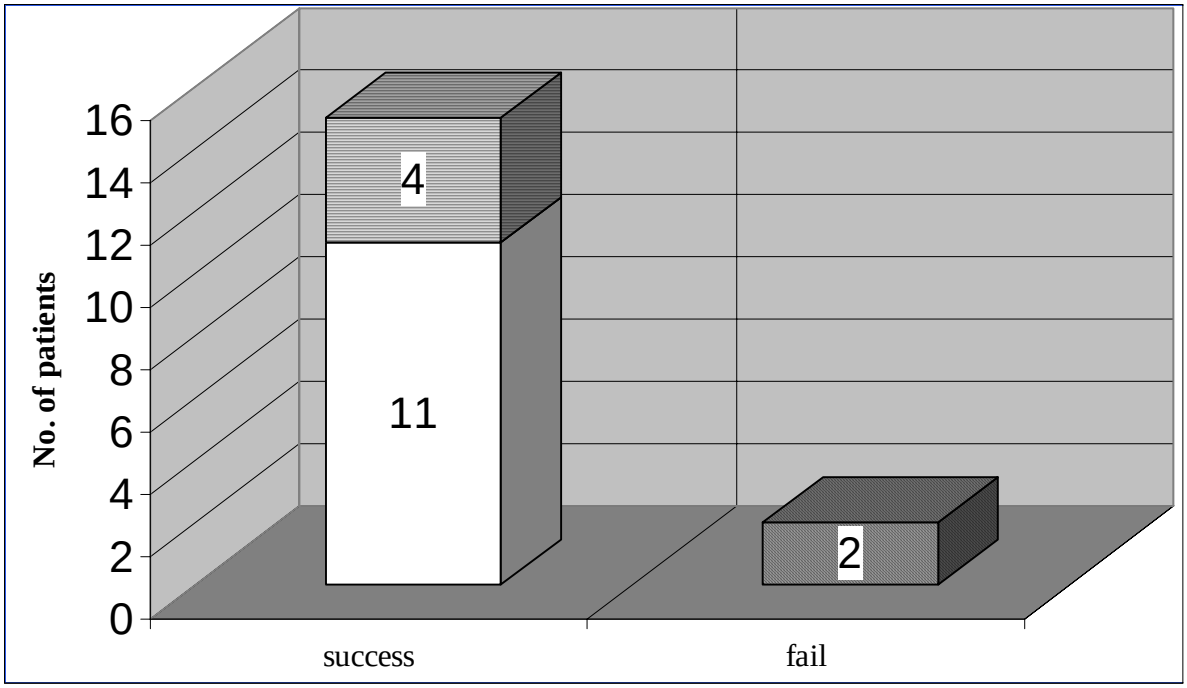
Excluded were those with major congenital anomalies, life-threatening infections, recent haemorrhage (within the previous 72 hours), renal failure –as defined by urine output less than 1 ml/kg/hr and serum creatinine greater than 100 μmol/l, platelet counts of 80 000 per cubic milliliter or less, prolonged INR and APTT, and those kept nil by mouth. Total fluid intakes of those admitted into the study were reduced to 100 –120 ml/kg/day, diuretics and angiotensin converting enzyme (ACE) inhibitors were given as necessary, and syrup ibuprofen was given at 5mg/kg/dose q6h for the first day, then 5mg/kg bd for a period of 4 days. Babies were weighed prior to starting therapy and again at the end of therapy, stools were taken for occult blood and abdominal girths were measured.

Blood investigations (full blood count (FBC), blood urea and serum electrolytes (BUSE), renal and liver function tests) were performed. At the end of each course, they were reassessed clinically and via 2D echo and colour Doppler. The PDA treatment was classified as having failed if PDA was still noted on echo with an audible murmur, or succeeded if there was no detectable PDA on echo or a trivial flow noted without a detectable murmur and resolution of tachycardia and tachypnoea. If after 2 courses of oral ibuprofen, the PDA did not close, the infants were then offered alternate forms of therapy – either oral indomethacin or surgery. Informed consent was obtained from all parents whose children were involved in the study.

A total of 17 patients were enrolled into the study, 10 females and 7 male subjects. The average gestational age of our subjects was 32 weeks gestation (range 28 –34 weeks). The average birth weight was 1498.8g (range 760–

Table 1. Average and median gestational age, birth weights and age at which ibuprofen was administered

| | Range | Average/Median |
|---|---|---|
| Gestational age | 28 – 34 weeks | 31.47 / 32 weeks |
| Birth weight | 760 – 2250 g | 1498.8 / 1500 g |
| Age at which ibuprofen was 1st administered | 6 – 31 days | 15.35 / 13 days |




Legend:

represents patients whose PDA shut on the 1st course of ibuprofen.

represents those whose PDA closed after the 2nd course of ibuprofen.

represents those that failed 2 courses of ibuprofen.

Fig. 1. PDA closure with ibuprofen.

2250g) (see Table 1). 11 patients responded successfully with closure of their PDAs after one course of ibuprofen. A further 4 patients required a second course of ibuprofen, before successful closure of the PDA was achieved (see Figure 1). In all the 4 cases requiring a second course of ibuprofen, the PDA was noted to be smaller on echo after the first course. Two did not respond to the treatment. Of the 2 that did not respond, both were noted to be partially responsive as they became less tachycardic and could be weaned off ventilation. One responded to a course of oral indomethacin while the other failed all available oral medications and at three years of age had the PDA successfully occluded by detachable Flipper™ coils in our hospital, after the child's parents refused the option of surgery.

There were no complications such as abdominal distention, a significant rise in urea or creatinine, serum bilirubin, weight gain and bleeding

Table 2. Results obtained before and after ibuprofen therapy

| Parameters measured | At beginning of therapy (mean +/- SD; and range) | At end of therapy (mean +/- SD and range) |
|---|---|---|
| Serum Urea (mmol/l) | 5.2 ± 4.1; 1.0 – 14.0 | 3.5 ± 2.3; 1.0 – 7.9 |
| Serum creatinine (μmol/l) | 66 ± 14; 51 – 78 | 58 ± 10; 48 – 67 |
| Serum bilirubin (mmol/l) | 128 ± 79; 23 - 343 | 115 ± 70; 22 - 303 |
| Occult blood in stools | 1 patient | nil |
| Weight (gm) | 1487 ± 365; 890 – 2240 | 1488 ± 364; 892 – 2240 |

tendencies in 16 of the 17 patients (see Table 2). One was noted to have positive occult blood in stools collected on the first day of initiation of ibuprofen therapy, which was not present in further samples collected.

## 2. Discussion

The search for safe options for closure of the PDA in premature neonates led initially from ligation of the PDA (surgery), to the pharmacological use of indomethacin first given orally then IV, and now the trials of ibuprofen. The first suggestion that ibuprofen could be used was in 1995. Patel et al (13) showed that closure of the PDA in premature neonates with ibuprofen were achieved in their study subjects without perturbations in intracranial blood flow as opposed to those given indomethacin. This was followed by other studies mentioned previously.

The dose of ibuprofen in our study (5 mg/kg/dose qid, followed by 5 mg/kg/dose bd) was chosen based on the studies of oral ibuprofen done in older children that were published elsewhere (19,20), as at the time of the conduct of our study, there were little pharmacokinetic data available on oral ibuprofen in neonates. One study (Aranda et al (21), 1997) looked at the pharmacokinetics of IV ibuprofen given on the first day of life in ELBW babies prior to our study (and later by Van Overmeire et al in 2001 (22) at days 3 to 5 of life in VLBW). As was expected, the results of these studies revealed a prolonged half-life of IV ibuprofen. However, we still decided to utilize our dosing schedule at the time, as there were no comparable oral ibuprofen studies published nor was the oral bioavailability of the drug and the pharmacokinetics following oral dosing in older neonates (beyond the first week of life) known. Our neonates were generally started on ibuprofen later as compared to the published studies (the earliest being at Day 6 of life, with the range extending to 31 days, see Table 1) because they had to tolerate feeds and show clinical signs of haemodynamic compromise from the PDA. The oral formulation of ibuprofen was also mixed with the feeds, hence also possibly interfering with the absorption of the orally administered drug. This was partially substantiated in a later study by Sharma and colleagues (23). In their study of 23 VLBW infants who were provided a single dose of oral ibuprofen at 10mg/kg between 4 and 72 hours of life, a large interindividual variability was observed for plasma concentrations, elimination half-life (15.72 ± 3.76 hours) and area under the plasma concentration-time curve, which did not seem to be affected by variables such as gestational age, birth weight and sex. There was also no correlation between elimination half-life and gestational age. Hirt and her colleagues (24) later described the pharmacokinetics in preterm neonates reporting that while the volume of distribution did not change with increasing age, ibuprofen plasma clearance did, thereby decreasing the half-life with increasing postnatal age, and this was independent of gestational age, birth weight and sex as had been described by Sharma earlier. Ibuprofen metabolism is via the cytochrome P450 complex (specifically CYP2C9 and CYP2C8). It is barely detectable at birth, but increases steadily in the first week of life and reaches to a third of the adult value in the first month. Hence, based on their study, they proposed that with increasing postnatal age, a higher dosing regimen should be prescribed: 10mg/kg followed by two consecutive 5 mg/kg doses for those less than 70 hours of age, 14, 7, 7 mg/kg for neonates between 70 hrs and 108 hrs, and 18, 9, 9 mg/kg/day for those more than 108 hrs of postnatal age. We employed a period of five days, based on the practices of Kumar and Yu (2) who proposed a more prolonged low dose course of indomethacin as being more effective with minimal side effects, hence, our choice for a 5 day course. In one of our test subjects, a dose of 4 mg/kg/tds was inadvertently administered and showed no effect on the PDA, with the patient remaining in heart

failure. But with the subsequent corrected dosing, the PDA was shut completely, with complete resolution of symptoms. With 5 mg/kg/dose dosing regimen of orally administered ibuprofen, we managed to achieve closure in 11 patients (65%) after 1 course, and 4 additional patients after a second course of ibuprofen (a total of 15 out of 17 or 88%) of the 17 patients enrolled into this study. Only one subject had occult blood present in stools that was noted at the beginning of the study even before ibuprofen was administered and was most likely unrelated to ibuprofen. There is also a theoretical risk of hyperbilirubinemia in children receiving ibuprofen, as ibuprofen displaces bilirubin from its binding sites in blood proteins but in our study this was not realized.

Despite the success and safety of oral ibuprofen, our study is small, consisting of only 17 patients. There are also a few studies detailing the use of oral ibuprofen for the closure of the PDA, the first in a letter published in Indian Paediatrics (25), followed by two studies done in Thailand, an abstract and also another study examining oral ibuprofen versus IV ibuprofen, published in Pediatrics, which also mentioned success of using oral ibuprofen in the closure of PDA. In the first study, they administered ibuprofen early at around day 3 to 5 of life and only if the premature neonates showed signs of heart failure. Dosing however, was 10 mg/kg as first dose followed by 2 further doses of 5 mg/kg at 12 hourly intervals, their success rate paralleled ours with closure achieved in 90% of their cases. The second and third were trials done comparing oral ibuprofen and indomethacin. Supapannachart et al (26) compared 18 babies less than 34 weeks of gestational age with PDAs and who were randomly assigned treatment, to either oral or IV indomethacin vs oral ibuprofen. They found comparable closure rates in their small sample, with the ibuprofen group having better urine outputs. Chotigeat and his colleagues (27) compared randomly assigned oral ibuprofen and IV indomethacin in 30 neonates with treatment started within 10 days of life and recorded success rates of 7 out of 15 for oral ibuprofen vs 10 out of 15 for IV indomethacin. Those that did not respond on the first attempt were provided another course of the drugs. There was a significantly higher usage of frusemide, and also an increased tendency towards NEC and surgical ligation for the indomethacin group, that did not reach statistical significance. A pilot study on the use of oral ibuprofen for closure of the PDA was published in 2008 as an abstract in Pediatrics (28). Heyman and his colleagues provided oral ibuprofen suspension to 22 preterm infants with a mean gestational age of 27.5$\pm$1.75 weeks, and whose mean weight was 979+266 g. In all these trials, treatment was 10 mg/kg of ibuprofen for the first day followed by 5 mg/kg given on the second and third days. Treatment was started earlier on the second day of life with closure achieved in all but one (95.5%). There were also no significant differences in serum creatinine before and after treatment as was in our study. Probably of interest is the recently published article by Cherif and his colleagues, (29) comparing oral versus IV ibuprofen and its effect on PDA in preterm neonates, while the numbers were small, 32 in each arm, his study demonstrated a better closure rate with oral ibuprofen versus IV ibuprofen (lysine) (84.3% vs 62.5%, respectively), with less adverse events (9.3% vs 31.2%). Although, p-values for adverse events were statistically significant, the 95% confidence interval for the relative risk did not support a significant difference.

Of interest, is a recently published study (30) examining the effect of oral ibuprofen on PDA in full term neonates. Orally administered ibuprofen was provided on those greater than three days of age at doses of 10 mg/kg/day for the first day, followed by two doses of 5mg/kg/day. There was a statistical significance between those treated versus those receiving placebo (73.3% and 42.9% closure rates respectively), and the PDA of those receiving ibuprofen was noted to close much earlier than those on placebo.

## 3. Conclusion

Despite the success in our pilot trial and other early trials, caution should still be advised when administering oral ibuprofen in premature babies who are critically ill (with signs of haemodynamic instability) and who are intolerant of orogastric feeds because of the increased risk of bowel ischaemia and NEC in this group.

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