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# Multiple Courses of Indomethacin and Neonatal Outcomes in Premature Infants

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## Abstract

The objective of this retrospective cohort study was to determine patent ductus arteriosus (PDA) closure rate with multiple short courses (three doses) of postnatal indomethacin and compare neonatal outcomes in infants who received two versus three courses of indomethacin for PDA closure. Infants <34 weeks' gestational age born between January 2000 and December 2004 at the University of Maryland Medical Center and who received two or more short courses of indomethacin were included. Outcome measures were ductal closure rate and neonatal outcomes. Of 61 infants who were identified to have received two or more courses of indomethacin, 26 infants closed their ductus after the second course (response rate, 42%). Of the 35 infants who failed ductal closure after two courses, 11 infants had their ductus ligated and 23 received a third course of indomethacin. Of 23 who received a third course, 10 closed their ductus (response rate, 43%). There was no significant difference in the incidence of chronic lung disease, severe retinopathy of prematurity, necrotizing enterocolitis, renal function, or mortality between infants who received two and those who received three courses of indomethacin. Infants exposed to three courses of indo-methacin had a statistically nonsignificant increased incidence of periventricular leukomalacia ($p = 0.08$; adjusted odds ratio = 4.8; 95% CI, 0.8–30) and remained in the hospital for a longer duration ($p = 0.02$) compared to infants exposed to two courses of indomethacin. We conclude that multiple courses of indomethacin may be associated with a ductal closure. However, the requirement for a third course may be associated with an increased risk of periventricular leukomalacia.

### Keywords

Multiple courses of indomethacin; Patent ductus arteriosus; Periventricular leukomalacia


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Indomethacin, a potent inhibitor of prostaglandin synthesis, has been routinely used to treat patent ductus arteriosus (PDA) in premature infants [10, 28]. However, approximately 20%–40% of premature infants have residual luminal flow or fail to close after the initial short course (three doses given every 12 h) of indomethacin [4, 12, 15, 28]. If the ductus fails to close after the initial course of indomethacin, surgical ligation of PDA and additional indomethacin treatment are two available options for the management of persistent PDA [20, 24]. It is not clear whether surgical ligation or multiple courses of indo-methacin should be the preferred treatment of PDA that fails to close after the initial short course of indomethacin [7, 19, 25]. The medical literature suggests that additional indomethacin treatment is unlikely to produce ductus closure for premature infants, if there is persistent Doppler evidence of ductal flow within 24 h after completion of the initial short course of indomethacin [17]. Contrary to this limited evidence, a recent survey of Neonatal Fellowship Program Directors in the United States reported that multiple courses of indomethacin, up to three, are commonly used for persistent PDA, after the initial course of indo-methacin [1]. This survey also reported that there is wide variation in the maximum number of courses of indomethacin used for the closure of persistent PDA and that most survey responders had lack of knowledge regarding the ductal closure rate with multiple courses of indomethacin [1].

Indomethacin is a known vasoconstrictor and has been shown to decrease mesenteric, renal, and cerebral blood flow in animals, which explains the possible risk for necrotizing enterocolitis (NEC), renal dysfunction, and periventricular leukomalacia (PVL), respectively [11, 18, 21]. The increase risk of chronic lung disease (CLD) is thought to be secondary to its inhibitory effects on surfactant production and stimulatory effects on proinflammatory mediators in the lung [5]. Postnatal indomethacin use is associated with intestinal perforation and acute renal dysfunction in premature infants [2, 14]. More recently antenatal indomethacin has been associated with PVL in premature infants (*Amin SB, in press*).

Indomethacin has a longer half-life in premature infants; this may lead to accumulation with multiple courses, with a theoretical risk of increasing the adverse effects with multiple exposures to indomethacin [27, 29]. To date, the usefulness of a third course of indomethacin, specifically the response rate of PDA closure and associated effects on neonatal outcomes, has not been reported in the literature. The purpose of this study was to determine the response rate of PDA closure with multiple courses of indomethacin and to compare neonatal outcomes between premature infants who received a maximum of two short courses of indomethacin and premature infants who received three short courses of indomethacin. This study was approved by the University of Maryland Institutional Research Review Board.

## Materials and Methods

A retrospective cohort study was performed to compare neonatal outcomes between premature infants who received a maximum of two courses of indomethacin and infants who received three courses of indomethacin for persistent PDA. The Neonatal Intensive Care Unit (NICU) database was used to identify infants who received one or more courses of indomethacin between January 2000 and December 2004. Our inclusion criteria included

infants <34 weeks of gestational age (GA) admitted to the NICU at the University of Maryland Medical Center, either inborn or transferred in within 24 h of birth; infants who had PDA diagnosed by echocardiography; and infants who received two or more courses of indomethacin for PDA. We excluded infants with ductal-dependent cardiac lesions and infants with antenatal PVL diagnosed by head ultrasound performed during the first week of postnatal life.

Premature infants in this study received a course of indomethacin after echocardiographic evidence of ductal flow was established. Indomethacin was not given in the presence of pulmonary hypertension (right-to-left ductal flow). The treatment regimen for the initial course consisted of three doses of indomethacin (0.2, 0.1, and 0.1 mg/ kg) 12 h apart. Within 48 h of completion of the initial course of indomethacin, infants were evaluated using echocardiography and color Doppler for the presence of ductal flow. If the PDA was persistent, a subsequent short course of indomethacin was initiated. The subsequent course involved three doses of 0.2 mg/kg at 24-h intervals. Within 48 h after completion of the second course of indomethacin, infants were re-evaluated. If the ductus was still open after the second course of indomethacin, one of two approaches was used during the study period, at the discretion of the attending neonatologist. The attending neonatologist either proceeded for surgical ligation or considered a trial with a third course of indomethacin. However, surgical ligation was always considered in the presence of contraindications to indomethacin use such as acute renal failure (creatinine level >1.8 mg/dl) or necrotizing enterocolitis. The ductal closure was defined as either complete anatomic closure by echocardiography or physiologic closure, which was a small to tiny PDA that was clinically asymptomatic. Indomethacin was not used for the prevention of intraventricular hemorrhage (IVH) during the study period. Ibuprofen was not used to close PDA during the study period.

A chart review was performed to collect information on clinical factors that may be associated with postnatal indomethacin use, evidence of ductal closure based on echocardiographic findings following each indomethacin course, and neonatal outcomes. Information on covariables that may be associated with neonatal outcomes was also collected. Neonatal outcomes included days to reach full feeds; NEC diagnosed based on x-ray findings of pneumatosis intestinalis or free air in the abdomen; isolated gastrointestinal perforation based on surgical reports; severe retinopathy of prematurity (ROP>stage 2 or stage 2 with plus disease); renal function based on creatinine values at 34 weeks postmenstrual age (PMA); CLD defined as oxygen requirement at 36 weeks' PMA; PVL based on reports by a pediatric radiologist on head ultrasounds performed at 1 month of chronological age and before discharge home; total number of hospital days to discharge; and mortality after the first week.

Statistical analysis was performed using a statistical program STATA (Stata Corp.). Continuous variables were analyzed using the Student t-test and categorical variables were analyzed using chi-square or Fisher exact test. A cutoff of $p < 0.1$ (two-tail analysis) was used to define association between multiple courses of indomethacin and individual neonatal outcomes. For neonatal outcomes associated with multiple courses of indomethacin, potential confounders ($p \leq 0.1$) were identified based on bivariate analysis. A regression model was built for each neonatal outcome that was found to be associated with multiple

courses of indomethacin. The full regression model included all identified potential confounders. Multiple regression analyses using backward selection method were performed using a p value ≤0.1 as a cutoff to keep confounders in the final regression model.

## Results

Of all the admissions to the NICU between January 2000 and December 2004, 280 infants <34 weeks of GA received one or more short courses of indomethacin for ductal closure. Of 280 infants, 21 infants were excluded (12 transferred 24 h after birth, 2 with PVL within first week, and 7 with ductal-dependent cardiac lesions). Of the remaining 259 infants, 198 closed ductus after the first course of indomethacin (76%). Sixty-one (24%) infants received two or more short courses of indomethacin.

### Response Rates (Ductal Closure Rates) to Multiple Courses of Indomethacin

Of those 61 infants who received a second course of indomethacin for failed closure after the first course, 26 infants closed the ductus arteriosus, for a response rate of 42%, with the second course. Of the remaining 35 infants who failed to close ductus with the second course of indomethacin, 23 infants were given a third course of indomethacin for persistent PDA, while 11 infants underwent surgical ligation. One infant had contraindication for both PDA ligation (active infection) and additional indo-methacin courses (creatinine level, 1.8 mg/dl). Four of 11 subjects underwent ligation because of NEC that developed after the second course of indomethacin. Ten of 23 infants closed ductus after the third course, for a response rate of 43%, with the third course of indomethacin. The cumulative response rate to three courses of indomethacin was 90% (234/259).

### Clinical Characteristics

Of 61 infants, 38 infants received a maximum of two courses and 23 infants received three courses of indo-methacin. Clinical characteristics of infants who received a maximum of two courses and those who received three courses of indomethacin are reported in Table 1. There was no significant difference in any of the variables including GA, birth weight, gender, race, antenatal indomethacin exposure, magnesium sulfate exposure, maternal use of illicit drugs, chorioamnionitis, asphyxia, respiratory distress syndrome (RDS), vasopressor (dopamine and dobutamine) use, and surgical ligation of PDA between the two groups. There was a trend for increased exposure to antenatal steroids for infants who received two courses of indomethacin compared to infants who received three courses of indomethacin. Similarly, there was a trend toward increased incidence of clinical sepsis among infants exposed to three courses of indomethacin compared to infants exposed to two courses of indomethacin.

There was no significant difference in any of the clinical characteristics including gestational age, birth weight, gender, race, antenatal indomethacin exposure, magnesium sulfate exposure, antenatal steroid exposure, maternal use of illicit drugs, chorioamnionitis, asphyxia, RDS, and use of vasopressors between infants who received surgical ligation (n = 11) and infants who received a third course of indomethacin after a failed second course of indo-methacin (n = 23), as reported in Table 2.

### Neonatal Outcomes After Multiple Courses of Indomethacin

Table 3 demonstrates neonatal outcomes as a function of exposure to two or three courses of indomethacin. There was no statistically significant difference in any of the neonatal outcomes between the two groups except for PVL and hospital stay among survivors. The incidence of PVL was higher in the group of infants who received three courses of indomethacin compared to the group of infants who received two courses ($p = 0.06$; unadjusted odds ratio = 5.4; 95% CI, 0.92–31). On controlling for antenatal steroid exposure and clinical sepsis, confounders identified based on bivariate analysis, the adjusted odds ratio for PVL was 4.8 (95% CI, 0.8–30; $p = 0.08$). There was also a significant difference ($p = 0.02$) in the total number of hospital days to discharge among survivors between the two groups. Infants who received three courses remained in the hospital longer than infants who received two courses of indomethacin.

There was no statistically significant difference in any of the neonatal outcomes between infants who received surgical ligation after a failed second course and infants who received a third course of indomethacin (Table 4). However, the incidence of PVL was higher in the group of infants who received a third course of indomethacin, compared to the group of infants who received surgical ligation after a failed second course ($p = 0.1$).

## Discussion

According to a recent survey of Neonatal Fellowship Directors, the majority of academic programs use multiple courses of indomethacin for the management of persistent PDA [1]. Although the use of multiple courses of indo-methacin is common, there are insufficient data in the literature regarding the response rate of PDA closure with multiple courses of indomethacin. The findings here suggest that both the second and the third course of indomethacin are independently associated with a 40% ductal closure rate among those who fail to close with a prior indomethacin course. Our findings also suggest that a cumulative ductal closure rate of 90% is achievable with three courses of indomethacin.

Although multiple courses of indomethacin may be associated with a good ductal closure rate, there may be risks associated with its use. The lack of sufficient evidence regarding this perceived risk may explain the lack of uniformity among academic programs regarding the maximum number of indomethacin courses that can be used for persistent PDA [1]. Indomethacin is a known vasoconstrictor and because of its prolonged half-life in premature infants, there is a possibility of cumulative adverse effects with multiple courses of indomethacin [27, 29]. Although indomethacin has been previously shown to cause acute renal dysfunction, we found no evidence of persistent renal dysfunction as evaluated by creatinine levels at 34 weeks of PMA, strongly suggesting that acute renal dysfunction, if it occurs, is transient and reversible [14]. Similarly, our findings suggest that a third short course of indomethacin may not be associated with an increased risk of NEC or intestinal perforation compared to two courses of indomethacin. The incidence of NEC with exposure to a third course of indomethacin may be spuriously low, as infants who developed NEC after the second course of indomethacin were not exposed to additional indomethacin but, rather, underwent surgical ligation for persistent PDA.

Indomethacin is also known to decrease cerebral blow flow velocity in premature infants (3). The possibility of a white matter injury, secondary to a decrease in cerebral blood flow, with the use of indomethacin has long been proposed. These speculations were raised when explaining the reported lack of beneficial effects on long-term neurological outcomes in the prophylactic indomethacin trial, despite a decrease in the incidence of severe IVH [26]. A recent meta-analysis of observational studies also reported an increased incidence of PVL following exposure to antenatal indomethacin in premature infants (*Amin SB, in press*). According to the existing literature, the reported incidence of PVL among premature infants is about 4%– 15% [23]. Our study findings of a 6% incidence of PVL in infants who were exposed to two courses of indomethacin compares well with the reported incidence in the literature. Our findings suggest that two courses of indomethacin may not be associated with an increased incidence of PVL. Although the difference in the incidence of PVL was not significant ($p < 0.05$) comparing two versus three courses of indomethacin, our findings of a clinically significant ($p < 0.1$) increase in the incidence of PVL with exposure to three courses of indomethacin is worrisome. The trend toward a clinically significant difference persisted, even after controlling for possible confounding factors. The difference in the incidence of PVL could also be secondary to persistent PDA in infants who received three courses; however, there are no data to support this relationship [7]. The biological plausibility and the strong association of antenatal indomethacin with PVL in premature infants support our findings of a weak to moderate association of a third course of postnatal indomethacin with PVL.

The trend for an increased incidence of CLD in infants who received three courses can be explained by the fact that 50% of infants failed to close after the third course and had persistent PDA for longer duration. Previous studies have associated CLD with persistent PDA [7, 8]. Another plausible mechanism is stimulatory effects of indomethacin on proinflammatory mediators in the lung [5]. A recent Cochrane review reported a trend for an increase incidence of CLD with a prolonged course (more than four doses) of indomethacin compared to a short course of indomethacin [13]. The trend for an increased incidence of CLD may also explain the longer hospital stay for infants who received three courses compared to infants who received two courses of indomethacin.

The preference to use a maximum of two courses, versus a maximum of three courses, should be based not only on risk-benefit ratio associated with each indomethacin course but also on how it compares with surgical ligation, an alternative treatment for persistent PDA. To date, a randomized study has not been reported comparing surgical ligation and multiple courses of indomethacin for persistent PDA in premature infants. Our findings suggest that a third course of indomethacin may be associated with an increased risk of PVL compared to surgical ligation after a failed second course of indomethacin for persistent PDA. However, a recent retrospective study has reported an increased incidence of CLD, severe ROP, and cognitive delay among infants exposed to indomethacin and surgical ligation compared to infants whose PDA was managed with indomethacin alone [16]. However, the group exposed to ligation was also exposed to significantly more indo-methacin doses compared to the group not exposed to ligation. The amount of indomethacin exposure (up to 0.91 mg) in the ligation group was similar to that achieved with three courses of indomethacin. The

study also failed to report the incidence of PVL. A separate retrospective study also demonstrated an increased incidence of CLD and hospital stay with surgical ligation, compared to indomethacin course, but failed to report the incidence of PVL [6]. In summary, our findings raise questions about the long-term safety of more than two courses of indo-methacin in premature infants. Our findings and the existing literature suggest that a second course of indo-methacin may be preferable to surgical ligation, after the failed initial course. However, surgical ligation may be preferable to a third course, after the failed second course of indomethacin, for the management of persistent PDA. There is also growing debate about whether or not to treat a refractory PDA, as there is always the possibility of a spontaneous closure or delayed surgical closure using a less invasive procedure, if the PDA does not close spontaneously. However, these questions should be carefully evaluated in a randomized clinical trial.

The major limitation of our study is the retrospective nature of the study, along with associated information and selection bias. The second limitation is the small sample size. It is possible that we may not have seen a significant difference in other neonatal outcomes because of inadequate power or type II error. Although this is a retrospective study, the findings are from a single unit over a 5-year period. There were no major changes in clinical practice during this study period to explain any of the findings. We believe this is the first report on neonatal outcomes after multiple short courses of indomethacin.

In summary, although our findings suggest a good ductal closure rate with multiple courses of indomethacin, the finding of an increased incidence of PVL with the use of a third course of indomethacin is worrisome. PVL is a known risk factor for abnormal long-term neurological outcome in premature infants [23]. A prospective, well-designed, and randomized study comparing surgical ligation and multiple courses of indomethacin is warranted to confirm the results of our observational study and reported findings of an increased incidence of CLD with surgical ligation. Alternatively, newer prostaglandin inhibitors such as ibuprofen may not be associated with PVL in premature infants and should be studied for the management of persistent PDA [22].

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## Table 1

Clinical characteristic of subjects as a function of two or three courses of indomethacin

| | 2 indomethacin courses (N = 38) | 3 indomethacin courses (N = 23) | p |
|---|---|---|---|
| Gestational age (wk)[a] | 25.9 ± 2.1 | 25.7 ± 2.5 | 0.7 |
| Birth weight (g)[a] | 849 ± 311 | 861 ± 331 | 0.9 |
| Gender (*male/female*) | 15/23 | 11/12 | 0.4 |
| Race (% African American) | 63 | 61 | 0.6 |
| Antenatal indomethacin (%) | 31 | 22 | 0.4 |
| Magnesium sulfate (%) | 50 | 61 | 0.4 |
| % of infants exposed to antenatal steroid | 84 | 65 | 0.08 |
| Maternal illicit drug use (%) | 13 | 17 | 0.7 |
| Clinical chorioamnionitis (%) | 21 | 9 | 0.3 |
| % of infants with Apgar <3 at 5 min | 16 | 9 | 0.7 |
| Sepsis (%) | 58 | 78 | 0.1 |
| Respiratory distress syndrome (%) | 79 | 78 | 0.6 |
| Vasopressors (%) | 66 | 78 | 0.3 |
| Surgical ligation (%) | 29 | 43 | 0.3 |

[a] Mean ± SD

## Table 2

Clinical characteristics as a function of surgical ligation or third course of indomethacin ± surgical ligation following *a* failed second course of indomethacin

| | Ligation after failed 2nd course (N = 11) | 3rd course ± ligation after failed 2nd course (N = 23) | p |
|---|---|---|---|
| Gestational age (wk)[a] | 24.8 ± 1.7 | 25.7 ± 2.5 | 0.2 |
| Birth weight (g)[a] | 726 ± 167 | 861 ± 331 | 0.12 |
| Gender (*male/female*) | 4/7 | 11/12 | 0.7 |
| Race (% African American) | 63 | 61 | 1.0 |
| Antenatal indomethacin (%) | 36 | 22 | 0.4 |
| Magnesium sulfate (%) | 45 | 61 | 0.4 |
| % of infants exposed to antenatal steroid | 54 | 65 | 0.7 |
| Maternal illicit drug use (%) | 9 | 17 | 0.6 |
| Clinical chorioamnionitis (%) | 27 | 9 | 0.3 |
| % of infants with Apgar <3 at 5 min | 27 | 9 | 0.3 |
| Sepsis (%) | 9 | 78 | 0.6 |
| Respiratory distress syndrome (%) | 91 | 78 | 0.6 |
| Use of vasopressors (%) | 91 | 78 | 0.6 |

[a]Mean ± SD

## Table 3

Neonatal outcomes as a function of two or three courses of indomethacin

| | Two indomethacin courses (N = 38) | Three indomethacin courses (N = 23) | p |
|---|---|---|---|
| Severe retinopathy of prematurity (%) | 20 | 22 | 0.8 |
| Intraventricular hemorrhage grade III/IV (%) | 29 | 43 | 0.2 |
| Periventricular leukomalacia (%) | 6 | 27 | 0.06 |
| Chronic lung disease at 36 wk of PMA (%) | 41 | 61 | 0.2 |
| Creatinine at 34 wk of PMA (mg/dl)[a] | 0.39 ± 0.08 | 0.41 ± 0.13 | 0.6 |
| Reached full enteral feeds (days)[a] | 33 ± 14 | 36 ± 15 | 0.4 |
| Necrotizing enterocolitis (%) | 16 | 9 | 0.7 |
| Isolated gastrointestinal perforation (%) | 13 | 9 | 0.3 |
| Mortality during NICU stay (%) | 37 | 26 | 0.4 |
| Days to discharge among survivors[a] | 72 ± 23 | 92 ± 34 | 0.02 |

*Note*: PMA, postmenstrual age; NICU, neonatal intensive care unit

[a]Mean ± SD

## Table 4

Neonatal outcomes as a function of surgical ligation or third course of indomethacin ± surgical ligation following failed second course of indomethacin

| | Ligation after failed 2nd course (N = 11) | 3rd course ± ligation after failed 2nd course (N = 23) | p |
|---|---|---|---|
| Severe retinopathy of prematurity (%) | 33 | 22 | 0.6 |
| Intraventricular hemorrhage grade III/IV (%) | 54 | 43 | 0.7 |
| Periventricular leukomalacia (%) | 0 | 27 | 0.13 |
| Chronic lung disease at 36 wk of PMA (%) | 55 | 61 | 1 |
| Creatinine at 34 wk of PMA (mg/dl)[a] | 0.35 ± 0.07 | 0.41 ± 0.13 | 0.2 |
| Reached full enteral feeds (days)[a] | 41 ± 10 | 36 ± 15 | 0.3 |
| Necrotizing enterocolitis (%) | 0 | 9 | 0.3 |
| Isolated gastrointestinal perforation (%) | 0 | 9 | 0.3 |
| Mortality during NICU stay (%) | 45 | 26 | 0.4 |
| Days to discharge among survivals[a] | 90 ± 16 | 92 ± 34 | 0.8 |

*Note*: PMA, postmenstrual age; NICU, neonatal intensive care unit

[a]Mean ± SD