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Indomethacin Use for the Management of Patent Ductus Arteriosus in Preterms: A Web-Based Survey of Practice Attitudes Among Neonatal Fellowship Program Directors in the United States

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Abstract

The objective of this study was to determine whether neonatal-perinatal fellowship programs (NFTP) in the United States vary in indomethacin use for the management of patent ductus arteriosus (PDA) in 28 week gestational age infants at birth. A 53-item web-based survey was sent to 84 NFTP directors who received prenotification, followed 2 weeks later by a reminder letter. A total of 56 NFTP directors responded (67% maximum response rate). Wide variation exists in the maximum number of indomethacin courses used to close ductus, use of indomethacin for reopened PDA beyond 14 days, ductal closure definition, contraindications before consideration of indo-methacin, interventions for contraindications, and reported ductal closer rate after each indomethacin course. Indomethacin therapy for symptomatic PDA and short course of indomethacin are common practices. Indomethacin use for the management of PDA in premature infants varies among NFTP directors. Practice attitudes may explain variations in ductal closure and ligation rates. Because practice variations may have implications for long-term outcome of vulnerable premature infants, studies relevant to the management of PDA in premature infants are needed.

Keywords

Indomethacin; Health care surveys; Premature infants

Patent ductus arteriosus (PDA) is extremely common, occurring in 50–75% of infants 28 weeks gestational age (GA) [19]. PDA is associated with increased risk of necrotizing

enterocolitis, chronic lung disease, pulmonary hemorrhage, and intraventricular hemorrhage (IVH) [10, 12, 24, 34]. Indomethacin is often used as a first line of treatment for PDA, with reported response rates greater than 60% in premature infants. However, studies have failed to provide conclusive results regarding the optimum duration, specifically short course (three dose) versus prolonged course (more than three doses) of indomethacin therapy [9, 20, 21, 26, 32, 33, 37]. Evidence is insufficient to support or refute the use of multiple courses (two or more courses) of indomethacin for the management of persistent PDA [23]. In addition, randomized trials conducted to date have varied in their definition of ductal closure based on echocardiographic findings. These variations in echocardiographic definitions of ductal closure have relevance for the interpretation of response rates in the literature and the need for further treatment [10, 13, 14, 20, 26, 28, 32, 33, 35, 37].

Although an initial indomethacin course will produce PDA closure in 60–80% of premature infants, the PDA reopens later in 6–53% of infants who initially respond to indomethacin [14, 17, 22, 30]. There also appears to be no consensus regarding the best approach for the management of reopened PDA in premature infants, specifically for a PDA that reopens after the first 2 weeks of postnatal life [25, 29]. The use of indomethacin may also be associated with complications such as renal insufficiency, bleeding diathesis, and focal intestinal perforation [12, 21, 22, 26, 31, 37]. Therefore, the use of indomethacin is contraindicated if there is oliguria, thrombocytopenia, or renal insufficiency. However, there appears to be no uniform criteria for the magnitude of oliguria, the degree of elevated creatinine levels, and the magnitude of thrombocytopenia [10, 13, 14, 20, 26, 28, 32, 33, 35, 37].

Institutional practice is expected to be based on existing evidence. If there is strong evidence for a particular treatment plan, one would expect it to be used by most academic medical institutions. However, if there is insufficient evidence in favor of a particular practice plan, one would expect institutional variations. The purpose of this Web-based survey is to determine whether neonatal-perinatal fellowship training programs (NFTPs) in the United States vary in (1) how ductal closure is defined based on echocardiography; (2) the timing, duration, and maximum number of courses of indomethacin used for the closure of PDA in infants 28 weeks GA; and (3) the criterion used for relative contraindications to indomethacin. The information gained will not only help identify areas in which further studies may be required but also support the development of practice guidelines by identifying approaches that are commonly used for the management of PDA by different NFTP directors.

Materials and Methods

Survey Questionnaire

A 53-item questionnaire was developed using the survey software Survey Monkey ([surveymonkey.com](https://www.surveymonkey.com), Portland, OR, USA). The questionnaire contained questions related to practice characteristics and approaches to the diagnosis and management of PDA in infants 28 weeks GA. Specifically, questions related to the timing, duration, maximum number of courses of indomethacin, use of indomethacin for reopened PDA after 14 days of postnatal life, criterion used for relative contraindications to indomethacin therapy, and interventions

used to treat relative contraindications were asked. The definition used to define ductal closure based on echocardiographic findings was also requested. Demographic information obtained included the number of infants ≥ 28 weeks GA admitted annually to neonatal intensive care units (NICUs), the predominant race of the patient population, the use of antenatal indomethacin for tocolysis, and the prophylactic use of postnatal indomethacin for IVH prevention at respective institutions. Questions specific to statistics included incidence of PDA and response rate of PDA closure to initial, second, and third course of indo-methacin at respective institutions. Finally, participants were asked whether their practice approach was based on experience or the literature. All questions except one (dose of indomethacin used for each course) were close-ended.

Although self-identification is considered the gold standard for reporting of race, reporting of predominant race of the patient population by some participants may have been based on observed race entered in medical records [16]. Previous studies have found very high agreement for African Americans and non-Hispanic whites between self-identified race and recorded race on administrative or medical records [6].

Pretesting and Sampling

During questionnaire development, cognitive interviews (pre-field testing) were conducted to refine the questionnaire with three directors of NFTP, two neonatologists, and one cardiologist from six different academic medical institutions. For our cross-sectional study, we used the only available U.S. perinatal directory (United States Neonatologists, Perinatologists, and Newborn Intensive Care Units Directory–2002; Section on Perinatal Pediatrics, American Academy of Pediatrics) to obtain e-mail addresses for NFTP directors. E-mail addresses were available for all 100 NFTP directors.

Web-Based Survey

A prenotification e-mail message announcing the survey was sent to each of the 100 NFTP directors in November 2004. Sixteen of 100 prenotification e-mails sent to NFTP directors did not reach intended recipients because of communication failure or incorrect e-mail addresses. A week later, an e-mail message that included the contents of the cover letter with a hyperlink to the Web-based survey was sent to 84 NFTP directors who received prenotification. Only those program directors who were sent the e-mail could connect to the hyperlink and respond to the questionnaire. Two weeks after the survey was opened, a reminder letter with a hyperlink to the survey was sent to all NFTP directors who received prenotification e-mails. We followed standard definitions of response rates from the American Association for Public Opinion Research [1]. The maximum response rate was calculated because there are no unknown NFTPs. The maximum response rate for the survey is the number of complete surveys divided by the number of surveys (complete plus partial) plus the number of nonsurveys (refusal and break-off plus noncontacts plus others). Prevalence rates with 95% confidence intervals (CIs) were calculated for each response. Data were analyzed using the chi-square test or Fisher's exact test. Prevalence ratios were calculated for clinical variables that were found to be associated with specific indomethacin therapy on bivariate analysis. A p value <0.05 was considered statistically significant. Statistical analysis was performed using Stata version 6 (Stata, College Park, TX, USA).

This study received prior approval from the institutional review board of the University of Maryland. Participants were informed that participation in the Web-based survey was voluntary, and that completion of the questionnaire implied consent to participate.

Results

After the initial opening of the survey, 45 NFTP directors responded. Following a reminder e-mail, an additional 11 responded for a total of 56, or a 67% maximum response rate. Institutional characteristics among those who responded are shown in Table 1. Ninety percent of the participants worked in an NICU with an annual admission of more than 50 infants 28 weeks GA at birth. As shown in Table 1, the use of antenatal indomethacin for tocolysis and use of indo-methacin for IVH prevention varied. Our survey found that approximately one out of four (23%; 95% CI, 13–33%) participating institutions used indomethacin for prevention of IVH. Although not shown, 90% of NICUs that use indomethacin for IVH prevention do not count this use toward therapy initiated for PDA.

Only 26% (95% CI, 15–37%) of participants routinely perform echocardiography to rule out PDA in an asymptomatic infant. Most participants reported that they consider direction and magnitude of ductal flow, as well as the size of ductus, when considering the use of indomethacin in an asymptomatic infant. Most participants will not treat if the size of the PDA is small (74%; 95% CI, 63–85%), the magnitude of ductal flow is small (71%; 95% CI, 59–83%), or the ductal flow is right to left (79%; 95% CI, 69–89%).

There is wide variation in magnitude levels of contraindications considered for indomethacin usage (Table 2). Among participants, 90% reported postponing the course of indomethacin until contraindications are absent. In the presence of thrombocytopenia, 82% (95% CI, 72–92%) will intervene and use platelet transfusion. Similarly, 52% (95% CI, 39–65%) of participants will use low-dose dopamine to improve renal function in the face of elevated creatinine levels. The use of furosemide to improve urine output is reported by only 39% (95% CI, 26–52%) of participants.

Seventy percent of participants reported that they believe in initiating treatment with indomethacin at the earliest postnatal age to improve PDA closure rate with indomethacin. However, only 9% of participants routinely use prophylactic indomethacin for silent (asymptomatic) PDA irrespective of the size of PDA and magnitude and direction of ductal flow (Table 3). Instead, 91% (95% CI, 84–98%) use indomethacin for symptomatic PDA (early or late symptomatic PDA). Among those who use prophylactic indomethacin for asymptomatic PDA, the reasons cited were to decrease the incidence of severe IVH and the annual ligation rate. Most participants use a short (three dose) course (94%; 95% CI, 91–97%) rather than a prolonged course of indomethacin (Table 3). Although not shown, 94% of participants based their decision to use a short or prolonged course on experience and the literature.

There is wide variation in how ductal closure is defined: 57% (95% CI, 44–70%) of participants defined ductal closure as occurring when there are no signs and symptoms of ductus, echocardiography reveals closed ductus, and color Doppler reveals no luminal flow.

The remaining 43% (95% CI, 30–56%) of participants defined ductal closure as having no signs and symptoms of ductus but may have diminished luminal ductal flow on Doppler.

Our survey found that most participants (74%; 95% CI, 63–85%) would consider further treatment for infants who have clinically responded to first course (become asymptomatic) but failed to close PDA based on echocardiography. The survey also found that 46% (95% CI, 33–59%) of participants use a maximum of two courses of indomethacin and 45% (95% CI, 32–58%) of participants use a maximum of three courses of indomethacin after failed indomethacin therapy. Five participants (9%; 95% CI, 2–16%) reported use of a maximum of one course of indomethacin for persistent PDA. Among those participants who use at least two courses of indomethacin, 97% based their use of a second course on experience and 85% based their use on the literature. Among participants who use up to three courses, 69% based their use of a third course on experience but only 35% reported use based on the literature. Among participants who use multiple courses of indomethacin, 72% (95% CI, 61–83%) do not use a higher total dose of indomethacin for second and third course of indomethacin compared to the first course during the first postnatal week. However, 55% (95% CI, 42–68%) will use a higher total dosage of indomethacin >7 post-natal days compared to the first postnatal week.

On comparing participants who use a maximum of two courses of indomethacin versus participants who use three courses of indomethacin, there was no difference in predominant race of patient population in NICU, annual admissions of infants <28 weeks GA in their respective NICU, incidence of PDA requiring treatment, timing and duration of indomethacin used, and definitions of ductal closure (Table 4). Approximately half (52%) of participants who used a third course considered a lower platelet count of 50,000/mm³ as a contraindication to indomethacin therapy compared to only 12% of those who used a maximum of two courses of indomethacin (prevalence ratio, 4.5; $p = 0.004$) (Table 4).

For PDA reopening after the initial successful indomethacin course, all participants reported that they consider use of indomethacin if the postnatal age of infant is <14 days. However, for reopened PDA after 14 days postnatal age, only 61% (95% CI, 49–73%) of participants use indomethacin (Table 3). Almost all participants (98%) reported use of indomethacin for reopened PDA based on experience, but only 67% reported the use was based on the literature.

There is wide variation in reported ductal closure rates after each indomethacin course, as shown in Table 5. Among those participants who use a third course of indomethacin, more than half (54%) did not know the response rate after the third course. All participants reported response to repeat indomethacin therapy for reopened ductus during the first 14 days, but only 67% of participants reported any response to repeat indomethacin course after the first 14 days.

Discussion

Our survey findings provide strong evidence that except for the timing and duration of indomethacin therapy, there are interinstitutional variations in the diagnosis and

management of PDA. Among NFTP directors, practice attitudes related to the use of indomethacin for the management of PDA in premature infants varied widely, including maximum number of courses of indomethacin, use of indomethacin for reopened PDA after 14 days, definition of ductal closure based on echocardiographic findings, magnitude of criteria used for relative contraindications to indomethacin therapy, and measures used to prevent or treat relative contraindications.

A previous meta-analysis of randomized studies comparing prophylactic indomethacin therapy versus indomethacin therapy for symptomatic PDA demonstrated short-term benefits with prophylactic therapy [13]. These benefits include a reduction in the incidence of PDA, need for surgical ligation of a PDA, and severe IVH without increased risk of intestinal or renal side effects [13]. Despite these reported short-term benefits, our survey findings suggest that most NICUs use indomethacin therapy for symptomatic PDA and not prophylactically for asymptomatic PDA. One plausible explanation for this difference could be the perceived possibility of spontaneous closure of asymptomatic PDA.

The other notable difference between the existing evidence and actual practice is the use of prophylactic indomethacin for IVH prophylaxis by 23% of programs. Previous studies have demonstrated that there is no long-term efficacy with regard to neurodevelopmental outcome with the use of indomethacin for IVH prophylaxis [13]. One plausible explanation for the difference between the evidence and actual practice could be a time lag between availability and implementation of evidence-based medicine as previously shown by the experience with antenatal steroids. There was wide variability in antenatal steroid use prior to the consensus conference, despite multiple randomized studies showing efficacy. Other explanations for inter-institutional variability include inadequacy of an evidence-based practice culture and poor communication of results to the clinical community. Moreover, it is not easy to change medical practices even when there is compelling evidence of benefit or lack of benefit [18, 27].

With regard to the duration of indomethacin therapy, randomized clinical studies neither support nor refute use of a short course (three doses given every 12 hours) of indomethacin over a prolonged course (more than three doses) [21]. Earlier studies suggested that a prolonged course of indomethacin therapy may be more effective in producing permanent ductus closure than the standard three-dose course when higher doses of indomethacin (0.2 mg/kg/day) are used with the prolonged course [20, 21]. In contrast, recent randomized studies, comparing a short course of indomethacin therapy with a prolonged course using smaller doses (0.1 mg/kg/day), have demonstrated that a prolonged course is no more effective than the standard three-dose short course in producing permanent closure and may in fact be associated with a higher incidence of focal gastrointestinal perforation [21, 26, 37]. Consistent with these findings, our survey found that most NICUs use a short course (three doses given every 12 hours) of indomethacin therapy rather than a prolonged course.

Whether surgical ligation or multiple courses of indomethacin is the preferred treatment of PDA that fails to close after the initial short course of indomethacin has not been well studied. The limited literature suggests that additional indomethacin treatment is unlikely to produce permanent ductus closure for infants who are ≥ 28 weeks GA if there is persistent

Doppler evidence of ductal flow within 24 hours after completion of the initial short course of indomethacin [23]. Our survey found that a large number of NICUs use multiple courses of indomethacin. In addition, we found wide variation in the maximum number of courses of indomethacin used for the closure of persistent PDA (46% two courses, 45% three courses).

Participants who use a third course of indomethacin also reported a higher prevalence of institutional antenatal indomethacin use compared to participants who use a maximum of two courses. Some studies have shown that use of antenatal indomethacin may increase the incidence of persistent PDA that is refractory to an initial postnatal indomethacin course [31]. The theoretical risk of an increase in major adverse effects, such as periventricular leukomalacia and focal gastrointestinal perforation, remains with cumulative indomethacin exposure during the antenatal and postnatal period [2, 4]. To date, the usefulness of the third course of indomethacin, specifically the response rate of PDA closure and associated adverse effects, has not been reported in the literature. Our survey found that there is wide variation in the reported use of indomethacin for reopened PDA after the first 14 days. Interinstitutional variation in the use of multiple courses of indomethacin and in the management of reopened PDA could be explained by the lack of evidence since most NICUs that use indomethacin for reopened PDA justified this use based on experience and not on the literature.

Our survey found a wide variation in reported ductal closure rate for each course of indomethacin. Although the accuracy of reported ductal closure rate for each course of indomethacin is unknown, the fact that more responders did not know the response rate with increasing number of courses of indomethacin suggests that the use of multiple courses of indomethacin, specifically the third course, has not been well studied. The variation in reported response rate to the first course may be partially explained by differences in the use of antenatal indomethacin, antenatal steroid, and how ductal closure is defined. Since the definitions used have relevance to the need for further treatment, there is a need to determine the clinical implications of a diminished ductal flow in the absence of symptoms. The survey also found that there is wide variation in the magnitude of contraindications considered acceptable before consideration of indomethacin therapy. The variation in the magnitude of relative contraindications used by different NFTP directors may explain some of the variation seen in the use of two versus three courses of indomethacin. For example, compared to participants who reported use of three courses for persistent PDA, participants who use a maximum of two courses consider a higher threshold level of platelet count as a contraindication to indomethacin therapy. The variation found regarding use of interventions such as low-dose dopamine and furosemide to improve renal function and urine output, respectively, may be explained by inconclusive evidence in the literature [5, 8].

We selected a Web-based survey mode because of the ability for rapid response, much lower cost compared to postal mail, and reduction of data entry errors [7, 36]. The cost involved was only \$40 to keep the survey active for 2 months. The response rate we observed is comparable to reported response rates from other Web-based surveys of physicians and surveys involving neonatologists [7, 15, 36]. Response rates for physician surveys are on average more than 10% lower than those for nonphysician surveys and have declined during the past decade [3, 11]. Due to limited resources, we were not able to employ multiple

modes to further improve our response rate. We did not solicit identifying information from the participants per institutional review board policies for exempt research, and therefore we were not able to target nonresponders. Previous studies of nonresponse to pediatrician surveys have found that low response rates are not necessarily an indicator of response bias [11].

We included NFTP directors from all regions of the United States in order to minimize selection bias. One limitation is that NFTP directors who participated in our survey may not accurately represent practice attitudes of all neonatologists in respective institutions. Another limitation is that there may exist differences between stated practice (what people state they do) and actual practice (what is actually done). Despite these limitations, the findings reflect the attitudes and practices of neonatologists in training programs, who disseminate this information to their trainees.

Because variations in practice attitudes that are due to insufficient evidence may have important implications for long-term outcomes of these vulnerable premature infants, there is a need to conduct studies on the use of multiple courses of indomethacin for PDA closure and the use of indomethacin for reopened PDA beyond the first 2 weeks. In addition, there is a need to determine the clinical implications of a diminished ductal flow in the absence of symptoms and define the magnitude levels of contraindications used for indomethacin therapy. Pending safety data from well-designed randomized clinical trials, we recommend that the third course of indomethacin be used only for infants with symptomatic PDA who are too unstable for surgical ligation.

Findings from our study can be used to promote the development of consensus regarding timing and duration of indomethacin therapy until future large-scale randomized studies provide more definitive results. Most institutions surveyed favor a short course of indomethacin over a prolonged course of indomethacin, and they favor the use of indomethacin for symptomatic PDA over prophylactic use for silent PDA. We recommend use of short course of indomethacin over a prolonged course of indomethacin for PDA closure. We do not recommend prophylactic indomethacin for silent PDA because of the possibility of spontaneous closure of asymptomatic PDA and lack of long-term benefits with prophylactic indomethacin. Individual NICUs may be encouraged by our findings to discontinue use of indomethacin for prevention of IVH.

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Table 1Characteristics of the reported neonatal intensive care units (NICUs; $n = 56$)

Characteristic	% of NICUs (participants)
Infants 28 weeks gestational age admitted annually	
<50 infants	10
50–99 infants	44
>100 infants	46
Population predominant (>50%) of particular ethnicity	61
Antenatal indomethacin usage	70
Indomethacin for intraventricular hemorrhage prevention	23
Incidence of patent ductus arteriosus requiring treatment	
50%	60
>50%	35
Do not know	5

Table 2Reported magnitude of contraindications considered for indomethacin therapy ($n = 56$)

Contraindication	% of respondents reporting magnitude of contraindications considered acceptable before consideration of indomethacin therapy
Creatinine level (mg/dl)	
>1.8	54
>1.5	37
>1.2	9
Urine output (ml/kg/hr)	
<1	82
<1.5	11
<2	7
Platelet count/mm ³	
<25,000	6
<50,000	30
<75,000	34
<100,000	30

Table 3

Practice attitudes regarding timing, duration, maximum number of indomethacin courses, and indomethacin therapy for reopened ductus among participants ($n = 56$)

Characteristic	% of NICUs (participants)
Timing of indomethacin	
Prophylactic for silent PDA	9
Early symptomatic PDA with signs within the first 4 days of birth	73
Late symptomatic PDA	18
Duration of indomethacin	
Short course (3 doses)	94
Prolonged course (>3 doses)	6
Maximum number of indomethacin courses	
One course	9
Two courses	46
Three courses	45
Indomethacin used for PDA reopening after postnatal age 14 days	61

NICUs, neonatal intensive care units; PDA, patent ductus arteriosus.

Table 4

Practice parameters and multiple courses of indomethacin

	% of those giving two courses (<i>n</i> = 26)	% of those giving three courses (<i>n</i> = 25)	<i>p</i> value
NICU with >100 infants 28 weeks GA annually	50	52	0.9
Predominant race (Caucasian)	46	44	0.8
NICU with antenatal IND usage	78	95	0.1
NICU with incidence of PDA >50% in 28 weeks GA	34	25	0.2
PDA closure: Doppler shows diminished ductal flow	40	42	0.9
Prophylactic use of IND for PDA	8	12	0.6
Use of short course of IND	92	96	0.6
>50% PDA closure rate after initial course of IND	85	64	0.09
IND for asymptomatic PDA after failed initial course	69	80	0.4

GA, gestational age; IND, indomethacin; NICU, neonatal intensive care unit, PDA, patent ductus arteriosus.

Table 5Reported ductal closure rate after each course of indomethacin therapy ($n = 56$)

Characteristic	% of NICUs (participants)
Ductal closure rate after first course of indomethacin	
26–50%	19
51–75%	34
>75%	36
Do not know	11
Ductal closure rate after second course of indomethacin	
<20%	9
20–40%	32
>40%	34
Do not know	25
Ductal closure rate after third course of indomethacin	
<10%	14
10–20%	16
>20%	16
Do not know	54

NICUs, neonatal intensive care units.