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Indomethacin Prophylaxis for Preterm Infants: the Impact of Two Multicentered Randomized Controlled Trials on Clinical Practice

Ronald I. Clyman, M.D.¹, Shampa Saha, Ph.D.², Alan Jobe, M.D., Ph.D.³, and William Oh, M.D.⁴

¹ Cardiovascular Research Institute and Department of Pediatrics, University of California San Francisco, San Francisco, CA 94143;

²Research Triangle Institute, Research Triangle Park, North Carolina, 27709;

³Departments of Pediatrics and Division of Pulmonary Biology, Children's Hospital Research Foundation, University of Cincinnati, Cincinnati, OH, 45229;

⁴Department of Pediatrics, Women and Infant's Hospital, Brown Medical School, Providence, RI, 02905

Abstract

Objectives—Two multicentered RCTs in premature infants (Ment et al, 1994 and TIPP, 2001) found beneficial effects of indomethacin prophylaxis on the incidences of patent ductus arteriosus (PDA), PDA ligation, and severe intracranial hemorrhage (ICH). The Ment-trial recommended its use. The TIPP-trial failed to find a benefit in its primary outcome (improved survival/neurodevelopmental outcome). This negative result may have discouraged prophylactic indomethacin use.

Study Design—We used the NICHD Neonatal Network Registry to determine the association between the two trials and the use of prophylactic indomethacin. We also statistically assessed the assumptions that led to the TIPP trial's negative results.

Results—Use of prophylactic indomethacin among Network clinicians increased after publication of the Ment-trial and decreased after the TIPP-trial. Analysis of the TIPP-trial showed that the primary outcome's anticipated effect size ($\geq 20\%$) was too large; a smaller effect size ($< 3\%$) would have been more appropriate based on the incidence of ICH in their population, and its association with neurodevelopmental outcome..

Conclusions—Two multicentered RCTs were associated with changes in indomethacin prophylaxis. Following the Ment-trial, its use increased. Following the TIPP-trial, which reported negative results based on too large an anticipated effect size, its use decreased.

Keywords

patent ductus arteriosus; intracranial hemorrhage

Introduction

Little information exists about the effects of well-reported, “influential”, multicentered clinical trials on neonatal care. Preterm infants are at risk for developing several cardiopulmonary and neurological morbidities including PDA, pulmonary hemorrhage, severe (grades 3 and 4) ICH,

Corresponding author: Ronald I. Clyman, M.D., Box 0544, HSW 1408, University of California, San Francisco, 513 Parnassus Ave, San Francisco, CA 94143-0544, phone: (415) 476-4462, FAX: (415) 502-2993, clymanr@peds.ucsf.edu.

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cerebral palsy and mental retardation (1–5). During the 1980's several small, single-center, controlled clinical trials suggested that prophylactic administration of indomethacin (within the first 24 hr after birth) reduced the incidence of severe grades of ICH, symptomatic PDA and surgical PDA ligations (6–10). This led to a widely publicized, multicentered trial (Ment-trial) that confirmed the benefits previously observed in the smaller, single center trials (11, 12).

Although the decreased incidence of severe ICH might be expected to result in improved neurodevelopmental outcome among infants treated with prophylactic indomethacin, there have been lingering concerns about indomethacin's effects on cerebral perfusion and possible risks of brain ischemia (13–15). Therefore, a large, multicentered trial (TIPP-trial) was performed to evaluate the long term effects of prophylactic indomethacin on motor, sensory, and cognitive outcomes (16). The TIPP-trial examined a group of 1202 infants with birth weights <1000 gm. Its stated primary objective was to determine “whether the prophylactic administration of indomethacin improves survival without neurosensory impairment”. Its secondary goal was to evaluate “the effects of indomethacin on the incidence of PDA, pulmonary hemorrhage, chronic lung disease, necrotizing enterocolitis, intracranial abnormalities, and retinopathy of prematurity”. While confirming the previously reported (17) beneficial effects of prophylactic indomethacin on the incidence of PDA, PDA ligation, ICH (grades 3 and 4), and pulmonary hemorrhage (16,18), the trial failed to find a decrease in the incidence of death or neurodevelopmental abnormalities. Although not specifically stated, the trial's conclusion implied that the use of prophylactic indomethacin should be discouraged.

Indomethacin prophylaxis has merits with regards to its effects on such neonatal morbidities as PDA, PDA ligation, pulmonary hemorrhage and severe ICH (16–18). We questioned whether the negative conclusion of the TIPP-trial (regarding survival and neurodevelopmental outcome) may have been based on an anticipated effect size that was unrealistic for the population that was studied. We hypothesized that publication of these two trials would affect the use of prophylactic indomethacin in clinical practice. The objectives of our study were 1) to determine the association between the two trials and the use of indomethacin, and 2) to statistically assess the assumptions that led to the TIPP trial's negative results.

Methods

We examined the NICHD Neonatal Research Network Registry to determine if the use of prophylactic indomethacin (indomethacin use during the first 24 h among infants who survived beyond the first 12 h after birth) was affected by the Ment-trial and the TIPP-trial. This multicentered Registry was developed to survey practices and to assess morbidity and mortality rates. Data collection techniques and definitions have been previously described (19). Since indomethacin prophylaxis is used primarily in very low birthweight infants, we determined its use among infants born before 30 weeks gestation (with birthweights between 401–1250 g), who survived beyond the first 12 h after birth. Three different time periods were examined: Epoch 1 (the 3 years prior to publication of the Ment-trial (11): calendar years 1991–93), Epoch 2 (the 3 years after its publication: 1995–97), and Epoch 3 (the 3 years after publication of the TIPP-trial: 2002–04). Because of center turnover within the Network during this time period, only the 10 centers that were in the Network for all three epochs were included in data retrieval and analysis (see Acknowledgements for a list of the 10 centers). In epoch 1 (1991–1993), 4296 infants that delivered ≤ 30 weeks gestation (birth weights between 401–1250 g) and survived beyond the first 12 h after birth, were entered into the Registry. In epoch 2 (1995–1997), 4167 infants were entered, and in epoch 3 (2002–2004), 4421 infants were entered into the registry. The years 1998–2001 were excluded since several Network centers were participants in the TIPP-trial during those years.

Statistical Analysis

To assess the effect of publication of the two RCTs on the use of indomethacin, analyses were performed with the continuity adjusted X^2 test for categorical data and the t test, regression analysis, and analysis of variance for continuous data. Values are presented as mean $\pm$ SD. Logistic-regression models were used to evaluate the epoch-related risks for prophylactic indomethacin use. Potential maternal, perinatal, neonatal, and demographic risk factors along with the epochs were entered into the models as predictors of prophylactic indomethacin use. The factors included: maternal age, race, singleton, mode of delivery, antenatal steroid use, antenatal antibiotics use, pre-eclampsia, place of birth (inborn or outborn), gestation, birth weight, gender, small for gestational age, Apgar score at 1 and 5 minutes, surfactant use, and study center.

Logistic-regression models were also used to evaluate the effects of prophylactic indomethacin use and of epoch (in addition to the other factors listed above) on the incidence of neonatal morbidities (severe ICH, PDA, surgical PDA ligation and NEC). Since these morbidities increase with decreasing gestational age, we examined the effects of prophylactic indomethacin on their incidence in each of the following gestational age categories: a) ≤ 25 wks, b) 26–27wks, and c) ≥ 28 wks gestation.

Results

Prophylactic indomethacin use in the Neonatal Research Network Registry

Logistic regression analysis showed that only epoch, study center, gestation, birthweight, and inborn status were independently related to the use of prophylactic indomethacin. Prophylactic indomethacin use increased significantly between epoch 1 and epoch 2 (odds ratio [OR]: 50; 95% confidence interval [CI]: 38 – 63, $p < 0.0001$). Following publication of the TIPP-trial, prophylactic indomethacin use declined significantly between epoch 2 and epoch 3 (OR: 0.84; 95% CI: 0.73 – 0.97, $p < 0.015$). Considerable center variability was observed during the study periods in the use of prophylactic indomethacin. During epoch 2, six of the 10 Network centers were frequent users of indomethacin prophylaxis in infants delivered < 26 wk gestation (average use in the six centers was $72 \pm 29\%$); the other four centers used indomethacin prophylaxis infrequently ($5 \pm 7\%$) in these infants. Two of the six centers, that were frequent users of indomethacin prophylaxis in epoch 2, essentially discontinued its use during epoch 3 (prophylactic use in the 2 centers dropped from 32% in epoch 2 to 4% in epoch 3).

Use of prophylactic indomethacin in the NICHD Registry was associated with a significant reduction ($p < 0.0001$) in the incidence of PDA in each of the gestational age groups examined (≤ 25 wks, 26–27wks, and ≥ 28 wks gestation). However, a significant reduction in the incidence of PDA ligations was only observed among infants delivered before 26 wks gestation (OR=0.68; 95% CI: 0.51–0.90, $p < 0.01$). Similarly, the incidence of PDA ligations, among infants born before 26 wk gestation, dropped significantly between epochs 1 (18%) and 2 (15%), and rose again in epoch 3 (21%) in parallel with changes in the use of indomethacin prophylaxis. There was no association between indomethacin prophylaxis and severe grades of ICH or NEC in the Registry.

TIPP-trial analysis

The TIPP-trial tested the hypothesis that prophylactic indomethacin would improve survival without neurosensory impairment by at least 20%. We examined the assumptions that led to this hypothesis: It was unlikely that a difference in survival would have been expected since none of the 17 controlled trials of indomethacin prophylaxis (nor a meta-analysis of their results) published prior to the start of the TIPP trial, found any association between

indomethacin prophylaxis and survival, vision or hearing (8,17). The prior trials did demonstrate that prophylactic indomethacin decreased the incidence of grade 3/4 ICH. Since the incidence of cerebral palsy and cognitive delay at 18 months is significantly increased by the presence of grade 3/4 ICH (7-fold for cerebral palsy and 1.8-fold for cognitive delay) (Table 1) (1,2), it might be expected that prophylactic indomethacin would result in improved neurocognitive outcome. In the TIPP trial, prophylactic indomethacin use reduced the incidence of grade 3/4 ICH from 13% to 9% (16); however, the incidence of grade 3/4 ICH in the Control population was low (13%) to begin with. Therefore, the expected rates of improvement in cerebral palsy and cognitive delay at 18 months would only have been 1.6% and 0.8%, respectively (Table 1), well below the study's anticipated effect size ($\geq 20\%$).

Comments and Conclusions

We hypothesized that the positive conclusions of the Ment-trial would encourage the use of prophylactic indomethacin, whereas the negative conclusions of the TIPP-trial would discourage its use. Our findings are consistent with this hypothesis: use of prophylactic indomethacin in the Neonatal Research Network increased following publication of the Ment-trial and declined following publication of the TIPP-trial. Similar pattern can also be found in the distribution of vials of indomethacin (Indocin® I.V.) to United States hospital pharmacies during the same period (1993–2005). The average monthly distribution of Indocin® I.V. increased significantly from 1993 through June 2001, the period following publication of the Ment-trial; in contrast, the number of distributed vials declined significantly following publication of the TIPP-trial (personal communication, Dave Knocke, Ovation pharmaceuticals).

Since randomized controlled trials have shown that prophylactic indomethacin reduces the incidence of severe ICH, PDA and PDA ligations (8), we examined the NICHD Network Registry to see if there were any associations between the changing use of prophylactic indomethacin and neonatal morbidities. Use of prophylactic indomethacin in the Network was associated with a significant reduction in the incidence of PDA and the incidence of PDA ligations among infants delivered before 26 wks gestation, but not in the incidence of severe ICH. The occurrence of severe ICH is known to be multifactorial (20). Although our analysis of the association between prophylactic indomethacin and ICH was risk-adjusted for maternal and neonatal variables, unmeasured variables may have affected the odds of ICH when prophylactic indomethacin is used in open-labeled, nonrandomized clinical practice. It is noteworthy that the incidence of PDA ligation increased as the use of prophylactic indomethacin decreased following publication of the TIPP-trial. Surgical ligation of a PDA is associated with its own set of morbidities: thoracotomy, pneumothorax, chylothorax, infection, vocal cord paralysis, and profound hypotension (21).

Our second objective was to examine the assumptions that led to the TIPP-trial's negative results. The TIPP-trial hypothesized that prophylactic indomethacin would produce at least 20% improvement in its primary outcome (death or neurodevelopmental abnormality). Although a persistent, symptomatic PDA of months or years duration has been associated with increased mortality (22,23), a delay in ductus closure of several days has not been shown to affect survival (8,17). One would not have expected the TIPP-trial to find a difference in survival since none of the previous prophylactic indomethacin trials had observed an effect on survival (8,17). The inclusion of death in their primary outcome was necessary to account for its potential competing effect on the other component of the primary outcome: neurodevelopmental outcome. Previous studies have shown that indomethacin prophylaxis decreases the incidence of severe ICH (8), and that severe ICH is strongly associated with neurodevelopmental abnormalities (1,2). Therefore, it seems reasonable to expect that the TIPP-trial might have found a difference in neurodevelopmental outcome, even if there was

no difference in survival between the two study groups. The TIPP-trial investigators found that severe ICH was associated with poor neurodevelopmental outcome (1,16). However, the incidence of severe ICH was low in their study population. The TIPP-trial was powered only to detect an effect size of $\geq 20\%$. Our calculations (Table 1) show that the expected difference in neurodevelopmental outcome between the two groups was more likely to be less than 2%. Therefore, it is not surprising that they may have missed this small, clinically insignificant difference in neurodevelopmental outcome between the two groups.

The cerebral vasoconstrictive effects of indomethacin are frequently cited as a concern among neonatologists (13–15). However, neonatal indomethacin exposure has not been found to have a negative effect on cognitive outcome in 8 years follow-up studies (24). In addition, a recent Cochrane systematic review of the literature found that indomethacin prophylaxis may actually decrease rather than increase the incidence of periventricular leukomalacia (8). An association between indomethacin use and decreased white matter lesions has also been found on MRI (25,26). And, favorable neurodevelopmental outcomes have recently been reported among 4.5 and 8 year old children who were originally treated with prophylactic indomethacin in the Ment-trial in 1994 (27,28).

Several previously reported beneficial effects of indomethacin prophylaxis (8,17) were again observed in the TIPP-trial: reduced incidences of surgical PDA closure, early serious pulmonary hemorrhage, and severe ICH (16,18). These benefits were achieved without an increase in the incidence of other neonatal morbidities (e.g., necrotizing enterocolitis, gastrointestinal perforation, retinopathy, chronic lung disease, or cerebral white matter injury).

We suggest that clinicians take into account the following considerations when making a decision about whether to use prophylactic indomethacin: 1) two large randomized controlled trials (11,16) documented the beneficial effects of this intervention in reducing the incidence of early neonatal morbidities (severe ICH, PDA and PDA ligation), in the absence of clinically significant adverse effects; 2) the negative conclusions of the TIPP-trial may have been due to an anticipated effect size that was excessively large for the population studied; 3) less use of this intervention in the Neonatal Network was associated with an increased incidence of surgical PDA ligation; and 4) neuroimaging data (25,26) and longer term neurodevelopmental outcome data (24,27,28) are both reassuring with regards to a lack of adverse effects and possible benefits of prophylactic indomethacin on neurodevelopmental outcome. Indomethacin prophylaxis may be a reasonable choice in intensive care nurseries where ICH and PDA are frequent management problems.

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Members of the NICHD Neonatal Research Network Alan Jobe, M.D., Chairman, University of Cincinnati *Case Western Reserve University (U10 HD21364)*

Michele Walsh, M.D.

Avroy A. Fanaroff, M.B., B.Ch.

Nancy Newman, R.N.

University of Cincinnati (U10 HD27853)

Edward F. Donovan, M.D.

Vivek Narendran M.D., MRCP

Marcia Mersmann, R.N.

Emory University (U10 HD27851)

Barbara J. Stoll, M.D.

Ellen Hale, R.N.

Indiana University (U10 HD27856)

James A. Lemons, M.D.

Brenda Poindexter, M.D.

Diana Appel, R.N.

University of Miami (U10 HD21397)

Shahnaz Duara, M.D.

Charles R. Bauer, M.D.

Ruth Everett R.N.

University of New Mexico (U10 HD27881)

Lu-Ann Papile, M.D.

Conra Backstrom, R.N.

Stanford University (U10 HD27880)

David K. Stevenson, M.D.

Krisa Van Meurs, M.D.

Bethany Ball, B.S.

University of Tennessee at Memphis (U10 HD21415)

Sheldon B. Korones, M.D.

Henrietta Bada, M.D.

Tina Hudson, R.N.

University of Texas Southwestern Medical Center (U10 HD40689)

Abbot R. Laptook, M.D.

Walid Salhab, M.D.

Gay Hensley, R.N.

University of Texas - Houston (U10 HD21373)

Jon E. Tyson, M.D., MPH

Kathleen Kennedy, M.D., MPH

Susie Madison, R.N.

Wayne State University (U10 HD21385)

Seetha Shankaran, M.D.

Ganesh Konduri, M.D.
Geraldine Muran, R.N.
Women and Infants Hospital (U10 HD27904)
William Oh, M.D.
Barbara Stonestreet, M.D.
Angelita Hensman, R.N.
Yale University (U10 HD27871)
Richard A. Ehrenkranz, M.D.
Patricia Gettner, R.N.
University of Alabama at Birmingham (U10 HD34216)
Waldemar A. Carlo, M.D.
Namasivayam Ambalavanan, M.D.
Monica V. Collins, R.N.
Harvard University (U10 HD34167)
Ann R. Stark, M.D.
Kerri Fournier, R.N.
Duke University (U10 HD40492)
Ronald N. Goldberg, M.D.
Michael Cotten, M.D.
Kathy Auten, R.N.
Wake Forest University (U10 HD40498)
T. Michael O'Shea, M.D.
Robert Dillard M.D.
Nancy Peters, R.N.
University of Rochester (U10 HD40521)
Dale L. Phelps, M.D.
Ronnie Guillet, M.D., Ph.D.
Linda Reubens, R.N.
University of California at San Diego (U10 HD40461)
Neil N. Finer, M.D.
Maynard Rassmussen, M.D.
Wade Rich
Research Triangle Institute (U01 HD36790)

Abhik Das, Ph. D.

W. Kenneth Poole, Ph.D.

Betty Hastings

Carolyn M. Petrie, M.S.

National Institute of Child Health and Human Development

Rosemary Higgins, M.D.

Linda L. Wright, M.D.

James Hansen, M.D.

*members of the NICHD Neonatal Network VLBW Registry who participated in the data collection: Brown, Yale, Case Western Reserve, Wayne State, Indiana, Cincinnati, Miami, Stanford, University of Texas – Dallas, and Emory.

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Abbreviations

PDA

Patent Ductus arteriosus

ICH

Intracranial Hemorrhage (severe=grade 3,4)

ELBW

Extremely low birth weight infants

RCT	Randomized controlled trial
NEC	Necrotizing enterocolitis
NICHD	National Institute of Child Health and Development
TIPP	Trial of indomethacin prophylaxis in preterms

Table 1

Expected versus Observed neurological and cognitive outcomes in the TIPP-Trial. The EXPECTED incidence of cerebral palsy (or cognitive abnormality) for a particular treatment group were calculated by using 1) previously published rates of cerebral palsy (or cognitive abnormality) in extremely low birth weight infants with a grade 3/4 ICH and those without a grade 3/4 ICH ($ICH \leq 2$), and 2) the anticipated rates of grade 3/4 ICH in the individual treatment groups. The previously published rates of cerebral palsy and of poor cognitive outcome (mental developmental index (MDI) < 70) were obtained from Laptook et al and Schmidt et al (1,2). {The rates reported in these two studies were: incidence of CP among infants with an ICH (grade 3/4) = 45%; among infants with an ICH (grade ≤ 2) = 6.7%; incidence of MDI < 70 among infants with an ICH (grade 3/4) = 42%; among infants with an ICH (grade ≤ 2) = 23% }. The anticipated rates of grade 3/4 ICH in the two treatment groups were obtained from the TIPP Trial (16): ICH (grade 3/4) = 13%; ICH (grade ≤ 2) = 87%. The OBSERVED Incidences of CP and of MDI < 70 are the incidences that were reported in the TIPP trial (16).

TIPP-Trial: Expected versus Observed Neurodevelopmental Outcomes

CEREBRAL PALSY (CP)					EXPECTED*	OBSERVED
	Incidence (%) (CP) x (ICH ≤ 2)		Incidence (%) (CP) x (ICH 3/4)		Incidence (%) CP	Incidence (%) CP
Placebo (n=601)	6.7% x 87%	+	45% x 13%	=	11.7%	12%
Prophylactic Indomethacin (n=601)	6.7% x 91%	+	45% x 9%	=	10.1%	12%
COGNITIVE (MDI < 70)					EXPECTED	OBSERVED
	Incidence (%) (MDI < 70) x (ICH ≤ 2)		Incidence (%) (MDI < 70) x (ICH 3/4)		Incidence (%) MDI < 70	Incidence (%) MDI < 70
Placebo (n=601)	23% x 87%	+	42% x 13%	=	25.5%	26%
Prophylactic Indomethacin (n=601)	23% x 91%	+	42% x 9%	=	24.7%	27%

* The number needed to detect the **expected difference in cerebral palsy rates** between the two treatment groups ($\alpha = 0.05$ (1), $\beta = 0.2$ (1)) is greater than 6,000 patients per group.