The Risk of Necrotizing Enterocolitis After Indomethacin Tocolysis
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The Risk of Necrotizing Enterocolitis After Indomethacin Tocolysis

WHAT’S KNOWN ON THIS SUBJECT: Indomethacin tocolysis continues to be used despite little evidence of improved neonatal outcomes. The literature addressing complications of antenatal indomethacin frequently discusses its association with necrotizing enterocolitis; however, antenatal indomethacin is strikingly absent in literature addressing risk factors for this condition.

WHAT THIS STUDY ADDS: In this study, antenatal indomethacin was significantly associated with necrotizing enterocolitis in preterm infants in the first 15 days of life. If indomethacin tocolysis is used, subjects should be educated regarding risks and benefits and the neonatologist be made aware of fetal exposure.

abstract

BACKGROUND: Postnatal indomethacin is reportedly associated with an increased incidence of necrotizing enterocolitis (NEC) in preterm infants. Because indomethacin readily crosses the placenta, we hypothesized that antenatal indomethacin (AI) would increase the risk for NEC in preterm infants.

OBJECTIVE: The goal of this study was to explore the association between AI and NEC in preterm infants.

METHODS: Medical records of preterm infants, 23 to 32 weeks’ gestational age, without major congenital anomalies, were reviewed. Maternal and neonatal data were abstracted. Association of AI within 15 days before delivery (predictor variable) and classification of NEC according to modified Bell’s stage 2a or higher in the first 15 days after delivery (early NEC [primary outcome variable]) was explored by using bivariate analyses, multivariate logistic regression, and propensity score analysis.

RESULTS: Of 628 eligible infants, 63 received AI and 28 developed early NEC. AI exposure was significantly associated with multiple gestation, race, antenatal corticosteroids and magnesium sulfate, lower birth weight and gestational age, umbilical arterial catheter placement, respiratory distress syndrome, postnatal vasopressors and antibiotics, patent ductus arteriosus, sepsis, NEC, intraventricular hemorrhage, and mortality. On multivariable logistic regression controlling for covariates, AI was significantly associated with early NEC (adjusted odds ratio: 7.193 [95% confidence interval: 2.514–20.575]; number needed to harm: 5). The results remained significant when analyses were repeated using AI exposure within 5 days before delivery as a predictor variable; on analyses stratified according to gestational age; and on propensity score analysis.

CONCLUSIONS: AI was associated with NEC in preterm infants in the first 15 days of life in this study, as were multiple other clinical factors. Pediatrics 2011;128:e54–e62

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KEY WORDS
neonatal, necrotizing enterocolitis, tocolysis, indomethacin, outcomes, prematurity, number needed to harm

ABBREVIATIONS
NEC—necrotizing enterocolitis
AI—antenatal indomethacin
GA—gestational age
MgSO4—magnesium sulfate
SIP—spontaneous intestinal perforation
ANCS—antenatal corticosteroids
RDS—respiratory distress syndrome
PDA—patent ductus arteriosus
BPD—bronchopulmonary dysplasia
IVH—intraventricular hemorrhage
PVL—periventricular leukomalacia
CI—confidence interval

All authors made substantive intellectual contributions to this study, including substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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Necrotizing enterocolitis (NEC), the most common gastrointestinal emergency in premature infants, is characterized by bowel necrosis and multisystem organ failure. Prematurity, enteral feeding, bacterial colonization, and ischemic gut injury play central roles in its pathogenesis. Indomethacin, a nonselective cyclooxygenase inhibitor, reduces mesenteric blood flow and is reportedly associated with an increased incidence of NEC in preterm infants when administered postnatally. Because indomethacin readily crosses the placenta, we speculated that antenatal indomethacin (AI) may also increase the risk for NEC. A review of the literature addressing risk factors for NEC revealed a striking absence of reference to AI as a risk factor, although 1 study did report a lack of association between AI and NEC. In contrast, publications addressing the complications of tocolytic agents frequently reference the association of AI with NEC in premature infants, with both positive and negative associations being reported. Meta-analyses based on these studies also revealed contradictory results. The observation of NEC in the first week of life in several sick preterm infants with AI exposure prompted us to undertake this study of the association between AI and NEC.

METHODS

We performed a historical cohort study of preterm infants 23 to 32 weeks’ gestational age (GA) admitted to the NICU at Hutzel Women’s Hospital between January 1, 2004, and December 31, 2006, to investigate the association of AI exposure within 15 days before delivery (predictor variable) and NEC classified according to modified Bell’s stage 2a or higher in the first 15 days of life (early NEC). Early NEC was the primary outcome variable in the study.

In the preterm fetus and neonate, the plasma half-life of indomethacin is 3 times longer than in adults because of immature renal function, impaired metabolism, and enterohepatic recirculation. The mean (range) half-life of indomethacin is 21 (9–60) hours in neonates <1000 g and 15 (3–52) hours in neonates >1000 g. We hypothesized that AI administered within 15 days before delivery is a risk factor for the development of NEC in the first 15 days of life (early NEC) in preterm infants. We chose a cutoff of 15 days before or after delivery because this represents ~5 half-lives (considering the longest reported half-life in preterm neonates), the time needed to clear indomethacin from the body.

The study was approved by the institutional review board, with waiver of parental consent. Infants with major congenital anomalies, outborn infants, and those transferred out within the first 15 days of life without a diagnosis of NEC were excluded. Magnesium sulfate (MgSO4) is the tocolytic of choice in our obstetrics department. Indomethacin is used as the second-line tocolytic agent and is typically administered orally as a loading dose of 100 mg, followed by 25 to 50 mg every 6 hours for the next 48 hours.

NEC was defined as modified Bell’s stage 2a or higher and required radiologic evidence of pneumatosiis, portal venous gas, or pneumoperitoneum in addition to clinical and laboratory features of NEC. Because of the difficulty in distinguishing between NEC and spontaneous intestinal perforation (SIP) based on clinical parameters, infants who were later diagnosed with SIP based on intraoperative and/or histopathologic findings were included in the analysis. Trained research staff abstracted maternal and neonatal data from medical records and pharmacy databases. Maternal data included demographic characteristics; perinatal complications; receipt of MgSO4, AI, antenatal corticosteroids (ANCs), and antibiotics; mode of delivery; and placental histopathology. Neonatal data included birth weight, GA, Apgar scores, feeding history, diagnosis of NEC in the first 2 weeks and beyond, laboratory findings, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), sepsis, postnatal drugs (vasopressors, steroids, indomethacin, and caffeine), placement of an umbilical arterial catheter, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity.

Statistical Analyses

Data were analyzed using SPSS 18.0 (SPSS Inc, Chicago, IL). Significance was denoted with a P value of <.05. Categorical data were analyzed using the χ² test and Fisher’s exact test. Continuous data were analyzed using an independent 2-tailed t test. Multivariable logistic regression models were constructed to determine the association between the predictor (AI) and primary outcome variable (early NEC) after controlling for significant covariates. Covariates were retained in the model if they demonstrated an association with either the predictor or outcome variable (P < .10). Analyses stratified according to GA and propensity score analysis were used to account for the baseline differences between the AI exposure groups. Propensity score was computed as predicted probability of AI group membership from all significant confounding covariates using logistic regression and was entered as a variable in the prediction model.

RESULTS

Of the 659 preterm neonates (23–32 weeks’ GA), admitted to the NICU, 628 met eligibility criteria. Infants who were outborn (n = 2), had congenital anomalies (n = 25), or were trans-
ferred out by <15 days of age (n = 4) were excluded.

MgSO₄ and indomethacin tocolysis preceded delivery in 50% (n = 315) and 10% (n = 63) of preterm infants, respectively. Both MgSO₄ and indomethacin were administered in 52 pregnancies. Mean (95% confidence interval [CI]) duration of AI and interval between start of AI and delivery was 1.5 (1.1–1.9) and 3.5 (2.6–4.4) days, respectively.

Modified Bell’s stage 2a or higher NEC was diagnosed in 39 infants at some point during their hospital stay (6.2%). Surgery (peritoneal drain and/or laparotomy) was performed in 18 (46.2%), and the overall mortality rate in these infants was 25.6% (n = 10).

Of the infants diagnosed with modified Bell’s stage 2a or higher NEC, 72% (n = 28) presented in the first 15 days of life (early NEC). Of these infants, 16 (57%) required surgery and 8 died (29%). Infants with early NEC accounted for 89% of infants requiring surgery (16 of 18) and 80% of all deaths attributed to modified Bell’s stage 2a or higher NEC (8 of 10). Of the 16 infants with early NEC requiring surgical intervention, 2 were diagnosed as SIP and 14 were diagnosed as NEC.

Nine (32%) of 28 infants with early NEC had AI exposure within 2 weeks before delivery. The mean (SD) interval between AI administration to the mother and diagnosis of NEC in the preterm neonate was 8.7 (6.1) days (range: 2.8–22.7 days). In 8 of these 9 infants, the interval between the first administration of AI to the mother and diagnosis of early NEC in the preterm neonate was <14 days; in 1 infant only was this interval >15 days (ie, 22.7 days).

**Bivariate Analyses of Maternal and Neonatal Characteristics According to AI Exposure Status**

AI was significantly associated with multiple gestation, white race, administration of ANCS and MgSO₄, and cesarean delivery (Table 1). In neonates, AI was significantly associated with birth weight; GA; need for an umbilical arterial catheter, assisted ventilation, surfactant for RDS, and postnatal vasopressors; PDA and need for surgical ligation; sepsis in the first 15 days of life; BPD; grade III to IV IVH; overall mortality; and duration of hospitalization (Table 2). There was a significant association between AI and modified Bell’s stage 2a or higher NEC during the entire hospital stay and in the first 15 days. Infants with AI were more likely to have feeds withheld in the first 15 days of life; a higher proportion received some human milk feeds.

**Bivariate Analyses of Maternal and Neonatal Characteristics in Infants With and Without Early NEC**

AI exposure was strongly associated with early NEC (Table 1). Infants with early NEC were more likely to be of lower birth weight and GA; require an umbilical arterial catheter, assisted ventilation, and surfactant for RDS; receive prolonged empiric antibiotics; and have longer hospital stays and higher rates of mortality, BPD, grade III to IV IVH, and PVL.

**Multivariate Logistic Regression to Evaluate Association of AI and Early NEC**

Multivariate logistic regression was performed to evaluate the significance of AI exposure in predicting early NEC. Covariates included birth weight; race; maternal chorioamnionitis; maternal treatment with MgSO₄ and ANCS and their interaction with AI; 5-minute Apgar score <5; presence of an umbilical arterial catheter; use of surfactant for RDS; postnatal treatment with vasopressors, caffeine, or steroids; sepsis; feeds initiated in the first 15 days; type of oral feed (breast milk or formula); duration of empiric antibiotics after delivery; and need for surgical ligation of PDA. Significant predictors of early NEC in the adjusted analysis included birth weight, initiation of feeds in the first 15 days of life, formula feeds, dura-

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**TABLE 1** Maternal Characteristics Grouped According to AI Exposure and Early NEC

<table>
<thead>
<tr>
<th>Maternal Age, Mean (SD), Y</th>
<th>Indomethacin Tocolysis</th>
<th>Diagnosis of Early NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 585)</td>
<td>Yes (n = 63)</td>
<td>No (n = 600)</td>
</tr>
<tr>
<td>Maternal age, mean (SD), y</td>
<td>27.3 (7.0)</td>
<td>27.0 (5.6)</td>
</tr>
<tr>
<td>Gravida, mean (SD), n</td>
<td>4 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Multiple gestation, n (%)</td>
<td>128 (23)</td>
<td>38 (60)</td>
</tr>
<tr>
<td>Prolonged rupture of membranes, n (%)</td>
<td>183 (33)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Black race, n (%)</td>
<td>474 (84)</td>
<td>35 (56)</td>
</tr>
<tr>
<td>Maternal drug use, n (%)</td>
<td>127 (23)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Clinical chorioamnionitis present, n (%)</td>
<td>87 (15)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Diabetes during pregnancy, n (%)</td>
<td>49 (9)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Antibiotics before delivery, n (%)</td>
<td>530 (88)</td>
<td>43 (68)</td>
</tr>
<tr>
<td>ANCS, n (%)</td>
<td>457 (81)</td>
<td>63 (100)</td>
</tr>
<tr>
<td>Maternal indomethacin tocolysis, n (%)</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Interval between AI and delivery, mean (SD), d</td>
<td>3.5 (3.6)</td>
<td>3.7 (3.6)</td>
</tr>
<tr>
<td>Duration of AI, mean (SD), d</td>
<td>1.5 (1.6)</td>
<td>1.6 (1.6)</td>
</tr>
<tr>
<td>Maternal MgSO₄ administration, n (%)</td>
<td>283 (47)</td>
<td>52 (83)</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>340 (60)</td>
<td>49 (79)</td>
</tr>
<tr>
<td>Placental histopathology conducted, n (%)</td>
<td>536 (96)</td>
<td>61 (88)</td>
</tr>
<tr>
<td>Acute chorioamnionitis on placental pathology, n (%)</td>
<td>227 (40)</td>
<td>30 (48)</td>
</tr>
<tr>
<td>Acute funisitis on placental pathology, %</td>
<td>144 (26)</td>
<td>19 (30)</td>
</tr>
</tbody>
</table>

Early NEC was defined as modified Bell’s stage 2a or higher NEC diagnosed in the first 15 days of life.

* P < .001.

**Table footnote:** AI within 2 weeks before delivery.

+ P < .01.
tion of empiric antibiotics after birth, and AI exposure (Table 3). The adjusted odds ratio for the development of early NEC after AI was 7.193 (95% CI: 2.514–20.575). This translates to a number needed to harm of ~5 using the method described for case-control studies39 (ie, indomethacin tocolysis in 5 pregnant women will result in 1 additional case of early NEC in preterm offspring as a result of the treatment).

Because of the concern of an imbalance in GA and birth weight between the AI exposure groups, we performed a multivariable logistic regression stratified according to GA using 26 weeks as a cutoff. AI was a significant predictor of early NEC in both GA strata.

The multivariate logistic regression for the entire cohort was repeated using AI initiated within 5 days before delivery as the predictor variable. The results were essentially the same as those observed with AI administered within 15 days before delivery (Table 4).

### Propensity Score Analysis

After including the propensity score as a covariate in the prediction model using logistic regression, AI administered within 15 days (Table 5) or 5 days before delivery remained a significant predictor of early NEC.

### DISCUSSION

AI exposure in infants born preterm (23–32 weeks’ GA) was associated with significantly increased odds of devel-

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**TABLE 2** Neonatal Characteristics Grouped According to AI Exposure and Early NEC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Indomethacin Tocolysis</th>
<th>Diagnosis of Early NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 565)</td>
<td>Yes (n = 63)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>1241 (470)</td>
<td>884 (339)™</td>
</tr>
<tr>
<td>GA, mean (SD), wk</td>
<td>29 (3)</td>
<td>26 (2)™</td>
</tr>
<tr>
<td>Birth weight appropriate for GA, n (%)</td>
<td>492 (88)</td>
<td>61 (57)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>299 (53)</td>
<td>34 (54)</td>
</tr>
<tr>
<td>5-min APgar score &lt;5, n (%)</td>
<td>57 (10)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Presence of umbilical arterial catheter, n (%)</td>
<td>219 (39)</td>
<td>48 (78)™</td>
</tr>
<tr>
<td>Need for assisted ventilation in first 15 d of life, n (%)</td>
<td>269 (48)</td>
<td>42 (67)™</td>
</tr>
<tr>
<td>Duration of postnatal empiric antibiotics, mean (SD), d</td>
<td>3.4 (2.8)</td>
<td>4.2 (3.5)</td>
</tr>
<tr>
<td>Surface for RDS, n (%)</td>
<td>317 (57)</td>
<td>56 (93)™</td>
</tr>
<tr>
<td>Postnatal vasopressors in first 15 d of life, n (%)</td>
<td>146 (25.8)</td>
<td>31 (49.2)™</td>
</tr>
<tr>
<td>Postnatal steroids in first 15 d of life, n (%)</td>
<td>26 (4.6)</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Early postnatal caffeine in first 15 d of life, n (%)</td>
<td>161 (28.5)</td>
<td>25 (33.7)</td>
</tr>
<tr>
<td>Early postnatal indomethacin/ibuprofen in first 15 d of life, n (%)</td>
<td>47 (8.3)</td>
<td>7 (11.1)</td>
</tr>
<tr>
<td>Diagnosis of PDA, n (%)</td>
<td>115 (20)</td>
<td>23 (37)™</td>
</tr>
<tr>
<td>Ligation of PDA, n (%)</td>
<td>37 (7)</td>
<td>9 (14)™</td>
</tr>
<tr>
<td>Culture-proven sepsis in first 15 d of life (blood/spinal fluid), n (%)</td>
<td>81 (14.3)</td>
<td>20 (31.7)™</td>
</tr>
<tr>
<td>Age at initiation of feeds, mean (SD), d</td>
<td>2.6 (3.0)</td>
<td>3.9 (5.4)</td>
</tr>
<tr>
<td>Infants not fed in the first 15 d of life, n (%)</td>
<td>69 (12)</td>
<td>17 (27)™</td>
</tr>
<tr>
<td>Exclusive formula feeds, n (%)</td>
<td>271 (55)</td>
<td>13 (28)™</td>
</tr>
<tr>
<td>Diagnosis of NEC (modified Bell’s stage 2a or higher), n (%)</td>
<td>28 (5)</td>
<td>11 (18)™</td>
</tr>
<tr>
<td>Diagnosis of early NEC (modified Bell’s stage 2a or higher), n (%)</td>
<td>19 (3)</td>
<td>9 (14)™</td>
</tr>
<tr>
<td>Age at diagnosis of early NEC (modified Bell’s stage 2a or higher), mean (SD), d</td>
<td>7.6 (3.6)</td>
<td>6.2 (5.0)</td>
</tr>
<tr>
<td>Death during first 15 d of hospitalization, n (%)</td>
<td>66 (12)</td>
<td>17 (27)™</td>
</tr>
<tr>
<td>Death during initial hospitalization, n (%)</td>
<td>50 (16)</td>
<td>24 (38)™</td>
</tr>
<tr>
<td>Duration of hospitalization, mean (SD), d</td>
<td>37.8 (34.1)</td>
<td>50.1 (47.6)™</td>
</tr>
<tr>
<td>Grade III to IV IVH, n (%)</td>
<td>58 (10)</td>
<td>13 (21)™</td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>106 (19)</td>
<td>22 (35)™</td>
</tr>
<tr>
<td>NEC modified Bell’s stage 2a or higher after the first 15 d of life, n (%)</td>
<td>6 (1)</td>
<td>2 (3)™</td>
</tr>
<tr>
<td>Retinopathy of prematurity requiring treatment, n (%)</td>
<td>23 (4)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>PVL, n (%)</td>
<td>17 (3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Early NEC was classified as modified Bell’s stage 2a or higher NEC diagnosed in the first 15 days of life. c P < .05. n (%) 17 (3) 2 (3) 15 (3) 4 (14)™. a P < .01. b P < .001.

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**TABLE 3** Multivariate Logistic Regression Model Estimating Risk of Early NEC Using AI Initiated Within 15 Days Before Delivery as the Predictor Variable

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE of Estimate</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>-0.001</td>
<td>0.001</td>
<td>0.20</td>
<td>0.999 (0.997–1.000)</td>
</tr>
<tr>
<td>Feeds started in the first 15 d of life</td>
<td>-3.312</td>
<td>1.081</td>
<td>.002</td>
<td>0.036 (0.004–0.303)</td>
</tr>
<tr>
<td>Formula feeds</td>
<td>1.304</td>
<td>0.518</td>
<td>0.012</td>
<td>3.864 (1.336–10.161)</td>
</tr>
<tr>
<td>Duration of empiric antibiotics</td>
<td>0.148</td>
<td>0.062</td>
<td>0.16</td>
<td>1.160 (1.028–1.308)</td>
</tr>
<tr>
<td>AI</td>
<td>1.973</td>
<td>0.536</td>
<td>0.000</td>
<td>7.193 (2.514–20.575)</td>
</tr>
</tbody>
</table>

Early NEC was classified as modified Bell’s stage 2a or higher NEC diagnosed in the first 15 days of life. OR indicates odds ratio.
One of the most challenging aspects of obstetrics is balancing the risks of pregnancy prolongation for both mother and fetus versus the risks of prematurity. The American College of Obstetricians and Gynecologists recommends that use of tocolytics may prolong pregnancy for 2 to 7 days, allowing administration of ANCS to improve fetal lung maturity and maternal transport to a tertiary care facility; however, no clear “first-line” tocolytic agent is identified. β-agonists, atosiban, and indomethacin all reduce the incidence of delivery within 48 hours compared with placebo, but none has been shown to improve neonatal outcomes. The Society for Maternal-Fetal Medicine and the Royal College of Obstetricians and Gynaecologists recommend that it is appropriate to withhold tocolysis from women presenting in preterm labor because neonatal benefit has not been demonstrated. Despite the relatively small number of patients studied and lack of evident benefits, tocolytic treatment has become entrenched in practice.

MgSO₄, the most frequently used tocolytic in the United States, was also used more frequently in our study. AI was used as a tocolytic in 10% of pregnancies, which is lower than reported across the United States (20%). In contrast, indomethacin is the most frequently prescribed tocolytic in Canada (47.5%). The tocolytic efficacy of indomethacin has been shown in several prospective trials. Initial enthusiasm was tempered by reports linking AI exposure after 34 weeks’ gestation to premature ductus arteriosus closure. Fetuses <29 weeks’ gestation seemed to tolerate indomethacin better than older fetuses. This led to the use of indomethacin as a short-term, and in some places, first-line tocolytic before 34 weeks’ gestation.

Several retrospective case-control and cohort studies evaluating neonatal outcomes after short-term indomethacin therapy have shown conflicting results, with many reporting no adverse association and others describing an increased risk of IVH, PVL, BPD, NEC, and PDA refractory to medical therapy. However, most were small, underpowered case-control studies with incorporation of few matching characteristics that did not consistently evaluate specific neonatal outcomes; in addition, several were performed before technologic advances in neonatal care and widespread use of ANCS and postnatal surfactant. Of the 8 small, randomized controlled trials designed to evaluate tocolytic efficacy of indomethacin, 7 covered the period from 1976 to 1992, 5 failed to mention NEC as an outcome that was evaluated, 2 reported NEC as an infrequent outcome, and only 1 reported an increased risk for NEC and SIP after AI. One meta-analysis based on these studies also showed conflicting results. One meta-analysis based on observational studies reported an association between AI and NEC; the other meta-analyses based on randomized controlled trials alone or in combination with observational studies failed to demonstrate this association.

The conflicting results of these studies pose a dilemma for the practicing obstetrician and neonatologist in evaluating the risk/benefit profile of AI. In fact, it is this dilemma that prompted us to undertake this study. Although randomized controlled trials are the gold standard for investigating effectiveness and safety of interventions, alternatives are necessary when evaluating harmful effects that are infrequent. Therefore, we chose a cohort study design to evaluate the association of AI with a potentially serious adverse effect in the neonate: NEC. In contrast to previously reported studies, we defined modified Bell’s stage 2a or higher NEC occurring within the first 15 days of life as the primary outcome variable because AI exposure is likely to be a risk factor for...
NEC early in postnatal life. On the basis of pharmacokinetics of indomethacin in preterm neonates, 15 days defines an interval close to 5 half-lives (the time needed to clear indomethacin from the body and thus representing the period of risk for developing NEC). For the same reason, we defined AI exposure as administration of AI within 15 days before delivery. Our results supported the choice of cutoff of 15 days before and after delivery: The interval between administration of AI to the mother and diagnosis of early NEC was <14 days in 8 of 9 preterm infants who had both AI exposure within 2 weeks before delivery and early NEC. In only 1 infant was this interval >15 days (ie, 22.7 days). A temporal relationship between AI and adverse neonatal effects has been described in some studies, with increased risk for adverse effects when infants were delivered within 1 to 5 days of commencing indomethacin.14,26 In our study, the significant association of AI and early NEC persisted when AI exposure within 5 days before delivery was used as the predictor variable.

The significant association of early NEC with duration of antibiotic treatment after delivery and the protective effect of human milk for the risk of NEC observed in our cohort has been reported previously.50-61 In our cohort, there was no association between postnatal indomethacin and early NEC. Awareness of the association of postnatal indomethacin and NEC and the debate regarding the need for treatment of PDA has led to decreased use of postnatal indomethacin in our institution and may account for the observed lack of association with NEC in our study. In the literature, there are conflicting reports, with increased,4,5 decreased,62 and unchanged63-65 incidence of NEC being reported after postnatal indomethacin. Although an increased risk for NEC has been reported in black preterm infants, males, and after maternal cocaine use, we did not observe these associations.66-68 Similarly, we could not demonstrate a synergistic effect between ANCS and AI and fetal toxicity as has been reported previously.69 This failure is likely attributed to the fact that the majority of infants in our study were black (~80%), were exposed to ANCS (>80%), and were born to women who denied abuse of recreational drugs (74%). The clustering of NEC with other adverse neonatal outcomes such as chronic lung disease, grade III to IV IVH, PVL, and prolonged hospitalization, as seen in our cohort, has also been previously reported.19,70,71

The unique strength of our study is the inclusion of a large cohort of preterm infants in an era of widespread availability of ANCS, postnatal surfactant, and technologic advances in neonatal care. Changes in perinatal management over the years may have affected rates of potential complications associated with AI. A historic cohort study design including all preterm infants at 23 to 32 weeks' GA delivered over a defined period with comprehensive collection of maternal and neonatal data were ideally suited to investigate the association of AI with NEC. Cohort studies may better represent the spectrum of medical practice and be more effective in assessment of harmful outcomes that are infrequent than randomized controlled trials.72 Use of propensity score analysis is an additional strength of our study. Propensity scores are used to reduce bias in observational studies in which treatment groups may differ markedly with respect to observed pretreatment covariates.72 The propensity score, defined as the conditional probability of being treated given the individual's covariates, is used either as a single confounding covariate in the prediction model or for comparisons using matching or stratification. This results in unbiased estimates of treatment effects and creates covariate balance between groups.

Despite the strengths, there are limitations typically associated with historic cohort studies: inability to distinguish between causation and association, reliance on information in medical records; unmeasured covariates; and the fact that most of the preterm infants who are at greatest risk for NEC are also the ones most likely to be exposed to indomethacin tocolysis after MgSO4 tocolysis was ineffective (confounding by indication). Lastly, although logistic regression revealed an association between AI and NEC, we did not take into account the number of preterm deliveries averted by AI. Any study evaluating tocolytic agents should include assessment of adverse effects and benefits. However, if tocolytics are expected to delay delivery by 48 hours, allowing administration of ANCS and transfer to a tertiary center, then the increased incidence of NEC and the ensuing nutritional consequences, and high morbidity and mortality in the products of these pregnancies, may not justify the continued use of AI; rather, we need to look for safer, equally efficacious alternatives.

CONCLUSIONS

AI was significantly associated with NEC in preterm infants in the first 15 days of life and may contribute to morbidity and mortality in this group. A large multicenter cohort study is needed to corroborate the results of our study; the potential for significant harm to the preterm infant precludes consideration of a randomized controlled trial. In the meantime, indomethacin tocolysis should be used after carefully weighing the potential benefits and risks.
In cases where indomethacin tocolysis is used, patients should be educated regarding fetal risks and benefits and the neonatologist informed of fetal exposure to indomethacin at delivery.

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REFERENCES

2. Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medi:
   
25. Amin SB, Sinkin RA, Glantz JC. Metaanalysis

33. King J, Flennady V, Cole S, Thornton S. Cyclo-
44. Mercer BM, Merlino AA, Society for

42. ACOG Committee on Practice Bulletins,

35. Thalji AA, Carr I, Yeh TF, Raval D, Luken JA,

39. Bjerre LM, LeLorier J. Expressing the mag-

38. Walsh MC, Kliegman RM. Necrotizing

37. Kliegman RM, Walsh MC. Neonatal necrotiz-

36. US Food and Drug Administration. Sterile Indocin


46. Fox NS, Gelber SE, Kalish RB, Chasnoff JT. Cont-

47. Hui D, Liu G, Kavuma E, Hewson SA, McKay D,

48. Morales WJ, Madhav H. Efficacy and safety of indomethacin compared with magne-


50. Hayes E, Moroz L, Pizzi L, Baxter J. A cost

51. Hamermerman C, Glaser J, Kaplan M, Schim-

52. Soraisham AS, Dalgleish S, Singhal N. Ante-

53. Murata Y, Itakura A, Matsuzawa K, Ochumura A, Kokuma K, Mizutani S. Possible antenatal and perinatal related factors in develop-

54. Rebarber A, Cleary-Goldman J, Istwan N, Rhea D, Stanziano G, Saltzman D. The associ-

55. Besinger RE, Niebyl JR, Keyes WG, Johnson TR. Randomized comparative trial of indo-

56. Sawdy RJ, Lye S, Fisk NM, Bennett PR. A cost


58. Rebarber A, Cleary-Goldman J, Istwan N, Rhea D, Stanziano G, Saltzman D. The associ-

59. Carlin A, Norman J, Cole S, Smith R. Tocolyt-

60. Carlin A, Norman J, Cole S, Smith R. Tocolyt-

61. Sisk PM, Lovelady CA, Dillard GR, Gruber JK, O’Shea TM. Early human milk feeding is asso-

62. Soraisham AS, Dalgleish S, Singhal N. Ante-

63. Dollberg S, Lusky A, Reichman B, Patent duc-


65. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


68. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

69. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-

70. Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. Users’ guides to the medical lit-


73. Soraisham AS, Dalgleish S, Singhal N. Ante-


75. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


78. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

79. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


82. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

83. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


86. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

87. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


90. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

91. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


94. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

95. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


98. Stout G, Lambert DK, Baer VL, et al. Necrotiz-

99. O’Donovan DJ, Baetiong A, Adams K, et al. Necrotizing enterocolitis and gastrointestinal complications during the first week of life: a multicentered case-control and co-


