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Association of intrapartum drugs to spontaneous intestinal perforation: A single center retrospective review

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Abstract

Background: Spontaneous intestinal perforation (SIP) occurs commonly in extremely low gestational age newborns (ELGANs; < 30 weeks GA). Early, concurrent neonatal use of indomethacin (Neo_IN) and hydrocortisone (Neo_HC), is a known risk for SIP. Mothers in premature labor often receive indomethacin (Mat_IN) for tocolysis and steroids (Mat_S) for fetal maturation. Coincidentally, ELGANs may receive Neo_IN or Neo_HC within the first week of life. There is limited data on the effect of combined exposures to maternal and neonatal medications. We hypothesized that proximity exposure to these medications may increase the risk of SIP.

Design: We reviewed the medical records of ELGANS from June 2014 to December 2019 at a single Level III NICU. We compared antenatal and postnatal indomethacin and steroid use between neonates with and without SIP. Chi-Square, Student's t-test, Fisher's Exact test, and Mann-Whitney U tests were used for analysis.

Results: Among 417 ELGANs, SIP was diagnosed in 23; predominantly neonates <26 weeks GA (n = 21/126, 16.7%). Risk factors analysis focused on this GA cohort in which SIP was most prevalent. Mat_IN administration within two days of delivery increased SIP risk (OR 3.00, 95%Cl 1.25–7.94, p=0.036). Neo_HC was not independently associated with SIP (p=0.38). A higher proportion of SIP group had close temporal exposure of Mat_IN and Neo_HC compared to the non-SIP group, though not statistically significant (14% v. 7%, p=0.24).

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Conclusions: Peripartum Mat_IN was associated with increased risk for SIP in this small study sample. Larger studies are needed to further delineate SIP risk from the interaction of peripartum maternal medication with early postnatal therapies and disease pathophysiology.

Keywords

extremely low birth weight; spontaneous intestinal perforation; indomethacin; hydrocortisone; betamethasone; magnesium; neonate

Introduction

Spontaneous intestinal perforation (SIP) predominantly occurs in the first 2 weeks of life among extremely low gestational age newborns (ELGANS), and often before initiation of enteral feeds[1–3]. Beyond the known association with extreme prematurity, a variety of antenatal and postnatal interventions have been suggested as risk factors for SIP. Reported prenatal risks include treatment with antenatal steroids, non-steroidal anti-inflammatory agents (e.g., indomethacin), and magnesium therapy [4–10]. Suggested post-natal risk factors include combined prophylactic indomethacin and early hydrocortisone or dexamethasone therapy [10–15]. Most studies have analyzed data as dichotomous variables with little attention to the timing of treatment interventions. There is limited data on the potential adverse effects of combinations of antenatal and/or postnatal therapies co-administered within the last week of pregnancy and the initial first weeks of postnatal life in ELGANs [10, 11, 13]. Maternal medications readily cross the placenta to the fetus and may have persistent effects for several days after dosing or delivery [6]. In addition, given the known association of SIP with the combination of postnatal indomethacin and postnatal glucocorticoid exposure, we speculated that late Mat_IN coupled with early Neo_HC exposure might pose the same SIP risk. The purpose of this study was to retrospectively evaluate the combined effect of maternal and neonatal medication exposure as modifiable factors for SIP in ELGANs. We hypothesized that co-exposure to antenatal indomethacin and early postnatal hydrocortisone would increase the risk of SIP.

Methods

This retrospective study was conducted in a large academic level III NICU. Initially, we reviewed all neonates born at less than 30 weeks GA who were admitted to the NICU within 48 hours of birth from June 2014 to December 2019. We excluded neonates with major anomalies. We compared neonates with SIP to those without (non-SIP). Neonates diagnosed with SIP were treated with drain placement or laparoscopic surgery. For infant's treated with drainage placement SIP was diagnosed by: clinical signs of abdominal distention and/or discoloration of the abdomen, absence of systemic illness suggesting NEC, and an abdominal radiograph presentation of either a gasless abdomen or pneumoperitoneum without signs of pneumatosis or intestinal ischemia. For infant's who underwent laparoscopic surgery SIP was diagnosed by signs listed above and operative/histopathologic findings of perforation located in the ileum and on the antimesenteric border consistent with SIP[16–18]. All neonates with a diagnosis of NEC, including bowel perforation, were analyzed in the non-SIP group.

The preliminary review noted that 21 of 23 SIP cases were in neonates born at less than 26 weeks GA among the ELGANs. We performed analyses only on the < 26 weeks GA neonatal cohort to specifically focus on those infants with the highest risk of SIP. Within the first 14 days of life, we analyzed the age of first administration, duration, and dosage of neonatal indomethacin, ibuprofen, dexamethasone, and hydrocortisone use. We do not routinely employ prophylactic indomethacin or ibuprofen, nor an early approach to the closure of the patent ductus arteriosus. We defined early neonatal exposure as medication initiated within the first 7 days of life. Maternal treatment with betamethasone, indomethacin, and magnesium sulfate was also captured, including the number of doses, total dosage, and timing relative to delivery up to 14 days prior to birth, with a specific focus on medication given 2 days prior to delivery. As we aimed to investigate possible synergism between early postnatal medications and persisting maternal medication in the neonate, we focused our analysis on maternal medications given 2 days prior to delivery and neonatal medication exposure within the first 7 days of life. Standard maternal and neonatal demographic data were collected as well as common morbidities associated with very preterm birth.

Statistical Analysis

We analyzed categorical data with Chi-square and Fisher's Exact tests. Normally distributed continuous data were analyzed by Student's t-test. We applied the Mann-Whitney U test for analysis of ordinal data and continuous data that were not normally distributed. All statistical analyses were performed using IBM SPSS statistics software version 26. Statistical significance was considered with a p-value less than 0.05.

Ethical Considerations

The University of Utah institutional review board approved this study with a waiver of parental consent. Trained research staff abstracted the required maternal and neonatal data via electronic medical records. Information was stored on a dual encrypted, password-protected database for analysis.

Results

Demographics

During the study period, 417 neonates born at less than 30 weeks GA and < 48 hours postnatal age were admitted to the NICU. We excluded 26 neonates due to major anomalies. Of 23 neonates diagnosed with SIP, 21/126 (16.7%) were < 26 weeks GA and 2/265 (0.7%) were ≥ 26 weeks. All subsequent results are for neonates < 26 weeks GA.

Maternal and neonatal characteristics by SIP versus no-SIP groups are shown in Table 1. None of the SIP neonates were born to mothers with preeclampsia ($p = 0.04$). A diagnosis of clinical chorioamnionitis and the presence of ruptured membranes greater than 7 days were more frequent in the SIP group but differences were not statistically significant. There were no differences between groups for gender, gestation, birth weight, or major neonatal

morbidities, except for an increased rate of severe intraventricular hemorrhage in the SIP group (grades 3 or 4).

The majority of SIP neonates (67%, n=14/21) were diagnosed within the first 7 days of life (median 6 days, range 1–36 days). Four neonates were diagnosed with a chronic intestinal perforation at autopsy or during surgery at a later time. However, those four neonates had clinical signs of intestinal dysfunction and feeding intolerance starting within the first week of life, raising suspicion that SIP occurred within that time but the diagnosis was delayed.

Prenatal and postnatal medication exposure

Among all prenatal medication exposures, Mat_IN exposure within two days of delivery was associated with a 3-fold increased risk of SIP (OR 3.00, 95%Cl 1.25–7.94, p = 0.036) (Table 2). Prenatal steroid and magnesium exposure, evaluated as independent variables, were not associated with SIP.

Compared to the non-SIP group, neonates with SIP had similar early HC exposure within the first week of life (Table 2). None of the four neonates treated with early indomethacin or dexamethasone had SIP.

Temporal proximity of prenatal and postnatal medication exposure

There was a higher proportion of SIP with the combined use of Mat_IN within 2 days before delivery and Neo_HC within the first 7 days of life compared to the non-SIP group, though not statistically significant enough to be considered as an association (14% vs. 7%, p = 0.24). (Table 2). Similarly, a higher proportion of the SIP group had concurrent exposure to maternal indomethacin and maternal steroids but no statistically significant association with SIP was found (29% vs 14%, p = 0.11).

Discussion

We report that antenatal indomethacin exposure within two days prior to delivery may increase the risk of SIP in neonates born at less than 26 weeks GA. This was found statistically significant however the small sample size prevented multivariate analysis and should be interpreted cautiously. We also had a two-fold higher rate of SIP with concurrent exposure of antenatal indomethacin and either maternal or neonatal steroid, this difference was not statistically significant. If the association is true, a larger sample size might be needed to demonstrate a statistically significant difference.

SIP risk was exclusive among <26 weeks GA neonates

The incidence rate of SIP in our unit was 4.6% among neonates born at < 30 weeks GA, aligning with the reported national incidence [3]. Among <26 weeks GA, our average SIP incidence was 17%. Vongbhavit et al. reported similar incidence rates of 20–30% among 24–26 weeks GA neonates [2]. The risk for SIP appears to be related to premature gastrointestinal development, as it is almost exclusively seen among extremely premature neonates born at less than 26 weeks GA. Prior research evaluating medication exposure as risk factors for SIP has yielded conflicting results [12, 17, 19]. It is important to note

that those studies included all neonates <30 weeks GA or <1000g BW. Differences in gastrointestinal maturation of neonates less than or more than 26 weeks GA may contribute to variation in relative risk for SIP associated with common antenatal and postnatal therapies.

Perinatal timing of medication exposure matters

The closer to delivery maternal medication is administered, the higher the serum concentration of the transplacental medication is in the neonate at the time of delivery. Each of the studied medications (betamethasone, magnesium, and indomethacin) crosses into the fetal circulation. The serum half-life of intramuscular betamethasone is relatively short in both mother and fetus (4.5 hours and 8.5 hours, respectively) [20]. However, due to genomic actions, there may be a sustained clinical effect extending to several days postnatally. The reported half-life for indomethacin is 2 hours in maternal circulation and 14 hours in fetal circulation [21]; it was also reported that some measurable drug levels have been found in the neonates bloodstream for up to two weeks [6]. The reported half-life for magnesium sulfate is 10 hours in maternal circulation, with fetal/neonatal clearance taking up to 50 hours [21]. As most SIP was diagnosed within 7 days of life in our population, one should account for the pharmacokinetics of prenatal and postnatal medication interaction in the maternal-fetal dyad.

The risks and benefits of antenatal indomethacin

Indomethacin is a prostaglandin inhibitor that may be used to delay preterm delivery while allowing the laboring mother to receive a full course of betamethasone. Hass and colleagues reported that prostaglandin inhibitors had the highest probability of delaying labor [18]. But a Cochrane Review meta-analysis found insufficient evidence to support the use of indomethacin as tocolysis [22]. Early tocolysis trials with indomethacin in the 1990s suggested safety [23], but neonatal benefits were not demonstrated [24]. More recent studies, including a meta-analysis, suggest that antenatal indomethacin might increase the risk for severe IVH, NEC, bronchopulmonary dysplasia (BPD), and periventricular leukomalacia [5, 6, 9, 25]. In earlier studies, SIP was not commonly distinguished from NEC [5]. Sood et al speculated that conflicting reports of antenatal indomethacin on neonatal morbidities might be related to the timing of exposure to delivery [6]. Indomethacin's ability to cross the placenta and relatively long half-life in the neonate allows for measurable drug levels in the neonate's bloodstream for up to two weeks post-delivery [6]. During the first week of life, we observed a three-fold increased risk of SIP in neonates < 26 weeks GA whose mothers received indomethacin within 48 hours of delivery.

The risks and benefits of postnatal Indomethacin

Indomethacin has been used widely in the early care of the neonate for patent ductus arteriosus treatment and IVH prophylaxis. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network reported no association between prophylactic indomethacin use and the increased incidence of SIP [17]. However, the Canadian Neonatal Network reported that postnatal indomethacin increased the risk of SIP by 2.4 folds (OR 2.4, 95%Cl 1.41–4.19) [12, 19]. Others have also reported an elevated risk of SIP with early indomethacin exposure [10, 12, 13, 26–28]. Lichtenberger

et al. observed in rat models that indomethacin led to intestinal mucosal injury and suppressed contractile activity in the ileum, posing a possible pathophysiologic link between indomethacin and SIP [29]. Our medical team has not prescribed postnatal indomethacin prior to 14 days of life since 2016. However, we did not observe a change in our SIP rate by avoiding early neonatal indomethacin use. This absence of a decreased trend in SIP may be secondary to maternal indomethacin administration.

The risk and benefit of postnatal Hydrocortisone

Early evidence suggested an increased risk of SIP with postnatal hydrocortisone or dexamethasone use [11, 13, 27, 30]. A meta-analysis by Morris et al reaffirmed this apparent risk for SIP noting the number needed to harm was 30, mainly when neonates were also being treated for patent ductus arteriosus (OR 1.69, 95%Cl 1.07–2.68, p = 0.03) [20]. We found no difference between the SIP and non-SIP groups when analyzing early postnatal hydrocortisone use as an independent variable in our small sample size.

The synergistic harmful effect of indomethacin and hydrocortisone

While significance was not shown in our study, the synergistic effect of hydrocortisone and indomethacin with SIP has been proven before. Separate groups have reported an increased risk of SIP with concurrent use of postnatal indomethacin and corticosteroids (hydrocortisone or dexamethasone) [11, 13, 27, 31, 32]. Stark et al. reported a significant rise in SIP with dexamethasone use alone (2%) but an even higher risk when used concurrently with indomethacin (19%) [32]. The PROPHET Trial was stopped early due to increased SIP in the HC arm, it was found that the combined exposure to HC and indomethacin was associated with a several-fold higher risk of SIP compared to placebo or treatment with HC or indomethacin alone [11]. Using a rat model, Gordon et al suggested that concurrent exposure to steroid and indomethacin synergistically increased the risk for intestinal perforation, which was mediated by the nitric oxide synthase pathway [14]. We observed a higher proportion of neonates with both prenatal indomethacin and early postnatal steroid treatment diagnosed with SIP, though this difference was not significant. However, our small sample might fail to detect any true association due to Type II error. A larger study is needed to more fully examine this association.

Limitations

As with any retrospective study, there is an inherent inability to distinguish between causation and association. Our research relies heavily on the accuracy of medical records. Unmeasured covariates may be a confounding factor, and the small sample size limited statistical power.

Conclusion

In summary, our results demonstrated an association between perinatal exposure to indomethacin within the last 2 days before birth and the occurrence of SIP in preterm neonates born at less than 26 weeks. Close perinatal exposure (antenatal and postnatal) of both indomethacin and steroid use may increase the risk of SIP in the most immature

preterm infant, though not significant in our analysis. Providers are encouraged to be vigilant in their evaluation for SIP with known antenatal indomethacin exposure. Avoidance of early neonatal steroid use may be a possible modifiable factor in the postnatal period. Further prospective investigation into the possible association of these factors is necessary with larger sample sizes.

References

1. Fisher JG, et al. , Mortality associated with laparotomy-confirmed neonatal spontaneous intestinal perforation: a prospective 5-year multicenter analysis. J Pediatr Surg, 2014. 49(8): p. 1215–9. [PubMed: 25092079]
2. Vongbhavit K and Underwood MA, Intestinal perforation in the premature infant. J Neonatal Perinatal Med, 2017. 10(3): p. 281–289. [PubMed: 28854518]
3. Durell J, et al. , Emergency laparotomy in neonates born at <26 weeks gestation: a neonatal network-based cohort study of frequency, surgical pathology and outcomes. Arch Dis Child Fetal Neonatal Ed, 2017. 102(6): p. F504–F507. [PubMed: 28468896]
4. Rattray BN, et al. , Antenatal magnesium sulfate and spontaneous intestinal perforation in neonates less than 25 weeks gestation. J Perinatol, 2014. 34(11): p. 819–22. [PubMed: 24901451]
5. Gordon PV, Swanson JR, and Clark R, Antenatal indomethacin is more likely associated with spontaneous intestinal perforation rather than NEC. Am J Obstet Gynecol, 2008. 198(6): p. 725; author reply 725–6. [PubMed: 18538165]
6. Sood BG, et al. , The risk of necrotizing enterocolitis after indomethacin tocolysis. Pediatrics, 2011. 128(1): p. e54–62. [PubMed: 21690109]
7. Rovers JFJ, et al. , The relationship between antenatal indomethacin as a tocolytic drug and neonatal outcomes: a retrospective cohort study. J Matern Fetal Neonatal Med, 2019: p. 1–7.
8. Norton ME, et al. , Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med, 1993. 329(22): p. 1602–7. [PubMed: 8232428]
9. Hammers AL, Sanchez-Ramos L, and Kaunitz AM, Antenatal exposure to indomethacin increases the risk of severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia: a systematic review with metaanalysis. Am J Obstet Gynecol, 2015. 212(4): p. 505 e1–13.
10. Sharma Hudak ML, Tepas JJ. Prenatal or postnatal indomethacin exposure and neonatal gut injury associated with isolated intestinal perforation and necrotizing enterocolitis. J Perinatol. 2010 Dec;30(12):786–93. [PubMed: 20410905]
11. Watterberg KL, et al. , Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics, 2004. 114(6): p. 1649–57. [PubMed: 15574629]
12. Stavel M, et al. , Effect of prophylactic indomethacin administration and early feeding on spontaneous intestinal perforation in extremely low-birth-weight neonates. J Perinatol, 2017. 37(2): p. 188–193. [PubMed: 27763630]
13. Attridge JT, et al. , New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. J Perinatol, 2006. 26(2): p. 93–9. [PubMed: 16319937]
14. Gordon PV, et al. , A neonatal mouse model of intestinal perforation: investigating the harmful synergism between glucocorticoids and indomethacin. J Pediatr Gastroenterol Nutr, 2007. 45(5): p. 509–19. [PubMed: 18030227]
15. Blakely ML, et al. , Postoperative outcomes of extremely low birth-weight neonates with necrotizing enterocolitis or isolated intestinal perforation: a prospective cohort study by the NICHD Neonatal Research Network. Ann Surg, 2005. 241(6): p. 984–9; discussion 989–94. [PubMed: 15912048]
16. Hwang H, et al. , Are localized intestinal perforations distinct from necrotizing enterocolitis? J Pediatr Surg, 2003. 38(5): p. 763–7. [PubMed: 12720189]
17. Kelleher J, et al. , Prophylactic indomethacin and intestinal perforation in extremely low birth weight neonates. Pediatrics, 2014. 134(5): p. e1369–77. [PubMed: 25349317]

18. Haas DM, et al. , Tocolytic therapy: a meta-analysis and decision analysis. Obstet Gynecol, 2009. 113(3): p. 585–94. [PubMed: 19300321]

19. Shah J, et al. , Intestinal perforation in very preterm neonates: risk factors and outcomes. J Perinatol, 2015. 35(8): p. 595–600. [PubMed: 25927271]

20. Moss TJ, et al. , Pharmacokinetics of betamethasone after maternal or fetal intramuscular administration. Am J Obstet Gynecol, 2003. 189(6): p. 1751–7. [PubMed: 14710109]

21. Tsatsaris V, Cabrol D, and Carbonne B, Pharmacokinetics of tocolytic agents. Clin Pharmacokinet, 2004. 43(13): p. 833–44. [PubMed: 15509182]

22. Reinebrant HE, et al. , Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database Syst Rev, 2015(6): p. CD001992. [PubMed: 26042617]

23. Loe SM, Sanchez-Ramos L, and Kaunitz AM, Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. Obstet Gynecol, 2005. 106(1): p. 173–9. [PubMed: 15994634]

24. Carlin A, et al. , Tocolytics and preterm labour. BMJ, 2009. 338: p. b195. [PubMed: 19264818]

25. Amin SB, Sinkin RA, and Glantz JC, Metaanalysis of the effect of antenatal indomethacin on neonatal outcomes. Am J Obstet Gynecol, 2007. 197(5): p. 486 e1–10.

26. Attridge JT, Clark R, and Gordon PV, New insights into spontaneous intestinal perforation using a national data set (3): antenatal steroids have no adverse association with spontaneous intestinal perforation. J Perinatol, 2006. 26(11): p. 667–70. [PubMed: 17024144]

27. Attridge JT, et al. , New insights into spontaneous intestinal perforation using a national data set: (2) two populations of patients with perforations. J Perinatol, 2006. 26(3): p. 185–8. [PubMed: 16493433]

28. Wadhawan R, et al. , Spontaneous intestinal perforation in extremely low birth weight neonates: association with indometacin therapy and effects on neurodevelopmental outcomes at 18–22 months corrected age. Arch Dis Child Fetal Neonatal Ed, 2013. 98(2): p. F127–32. [PubMed: 22684157]

29. Lichtenberger LM, et al. , Suppression of contractile activity in the small intestine by indomethacin and omeprazole. Am J Physiol Gastrointest Liver Physiol, 2015. 308(9): p. G785–93. [PubMed: 25721304]

30. Morris IP, Goel N, and Chakraborty M, Efficacy and safety of systemic hydrocortisone for the prevention of bronchopulmonary dysplasia in preterm neonates: a systematic review and meta-analysis. Eur J Pediatr, 2019. 178(8): p. 1171–1184. [PubMed: 31144162]

31. Paquette L, et al. , Concurrent use of indomethacin and dexamethasone increases the risk of spontaneous intestinal perforation in very low birth weight neonates. J Perinatol, 2006. 26(8): p. 486–92. [PubMed: 16791261]

32. Stark AR, et al. , Adverse effects of early dexamethasone treatment in extremely-low-birth-weight neonates. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med, 2001. 344(2): p. 95–101. [PubMed: 11150359]

Table 1.

Comparison of maternal and neonatal demographic by presence or absence of spontaneous intestinal perforation (SIP) in neonates less than 26 weeks gestation

	SIP (n=21)	no SIP (n=105)	p value
Maternal demographics			
Age (years)	29 ± 5	28 ± 6	0.63
Maternal Race/Ethnicity, n (%)			0.54
Caucasian	12 (57)	71 (68)	
African-American	1 (5)	2 (2)	
Hispanic	5 (24)	25 (24)	
Other	3 (14)	7 (7)	
Multiple gestations, n (%)	6 (29)	29 (28)	0.92
Chorioamnionitis, n (%)	8 (38)	20 (19)	0.55
Preeclampsia, n (%)	0 (0)	19 (18)	0.04
Chronic hypertension, n (%)	0 (0)	7 (7)	0.63
Diabetes, n (%)	1 (5)	9 (9)	0.56
IUGR, n (%)	0 (0)	11 (10)	0.21
Abruption, n (%)	3 (14)	15 (14)	0.92
Oligohydramnios, n (%)	1 (5)	13 (12)	0.68
Cerclage, n (%)	9 (43)	47 (49)	0.32
PROM >24 hours, n (%)	7 (33)	33 (33)	0.52
PROM >7 days, n (%)	6 (29)	14 (13)	0.08
C-section, n (%)	12 (57)	64 (61)	0.68
Neonatal demographics			
Male, n (%)	14 (67)	52 (50)	0.15
Birth Weight (g)	683 ± 89	669 ± 144	0.66
Gestational Age (weeks)	24.5 ± 0.7	24.6 ± 0.8	0.57
SGA, n (%)	2 (10)	15(14)	0.4
5 minute APGAR <5, n (%)	8 (38)	40 (38)	0.64
Inborn, n (%)	19 (91)	96 (91)	0.88
Severe IVH (Grade 3 or 4), n (%)	11 (52)	26 (25)	0.005
Severe ROP (stage 3), n (%)	4/12 (33)	30/65 (45)	0.85
Early Sepsis: confirmed, n (%); suspected, n (%)	3 (14); 8 (38)	13 (12); 42 (40)	0.56
Mortality, n (%)	14 (67)	37 (35)	0.63

[a]Data shown as median ± standard deviation

[b]Data shown as number (n) and percentage (%)

IVH intraventricular hemorrhage, ROP retinopathy of prematurity, IUGR intrauterine growth restriction, PROM premature rupture of membrane

Table 2.

Comparison of maternal and neonatal medication exposure by presence or absence of spontaneous intestinal perforation (SIP) in neonates <26 weeks gestation

	SIP (n=21)	No SIP (n=105)	P value	95% CI
Single medication exposure[a, b]				
Maternal Indomethacin	7 (33)	15 (14)	0.036	3.00 (1.25–7.94)
Maternal Steroid	12 (57)	64 (61)	0.74	0.85(0.34–2.08)
Neonatal HC	11(52)	44 (42)	0.38	1.53 (0.59–4.10)
Combined medication exposure[a, b]				
Maternal Indomethacin + Neonatal HC	3 (14)	7(7)	0.24	2.33 (0.61–9.97)
Maternal Indomethacin + Maternal Steroid	6 (29)	15 (14)	0.11	2.4 (0.77–6.58)
Maternal Steroid + Neonatal HC	5 (24)	28(27)	0.79	0.86 (0.32–2.51)

Data shown as number (n) and percentage (%)

OR, Odds ratio; HC, hydrocortisone

[a]Maternal therapy within 2 days of delivery

[b]Neonatal therapy within 7 days postnatal life