

Focal Small Bowel Perforation: An Adverse Effect of Early Postnatal Dexamethasone Therapy in Extremely Low Birth Weight Infants

Phillip V. Gordon, MD, PhD
Mary L. Young, MS
Diane D. Marshall, MD, MPH

OBJECTIVE:

We tested the hypothesis that early postnatal dexamethasone (EPD) increases the risk of focal small bowel perforation (FSBP) in extremely low birth weight (ELBW) infants.

STUDY DESIGN:

The techniques of meta-analysis were applied to studies evaluating EPD, which we identified through a systematic literature search. Studies were included if they were randomized, placebo-controlled trials of EPD, enrolled infants with birth weights ≤ 1000 g, and reported FSBP as an outcome variable. The Breslow-Day test was used to assess for homogeneity and a summary odds ratio was calculated using the Mantel-Haenszel exact method.

RESULTS:

Four studies, with a pooled sample of 1383 infants, were included in the primary analysis. The Breslow-Day test showed a p -value of 0.61, indicating homogeneity among the studies. FSBP was significantly higher in EPD treated infants [odds ratio 1.91, 95% confidence interval (CI) 1.21, 3.07; $p = 0.004$].

CONCLUSION:

EPD increases the risk of FSBP in ELBW infants.

Journal of Perinatology 2001; 21:156–160.

INTRODUCTION

Focal small bowel perforation (FSBP) has recently been recognized as a distinct disease entity in extremely low birth weight (ELBW) infants. Though still uncommon, multiple case reports and case studies published in the last decade suggest an increasing incidence

in the postsurfactant era.^{1–7} FSBP occurs independently of necrotizing enterocolitis and shares pathologic and clinical findings with small bowel perforations described in term infants.^{8–10} Typically, FSBP presents near the end of the first week of life in infants with birth weights less than 1000 g, occurring as a solitary lesion in the ileum, without surrounding inflammation or infection.^{11,12} Without surgical intervention, this disease results in peritonitis that can rapidly progress to fulminate sepsis and death.¹³ Surgical specimens contain segmental abscesses within the smooth muscle surrounding the site of the lesion, suggesting a focus for structural weakness.¹¹ However, the etiologic risk factors and pathophysiologic mechanisms associated with FSBP in ELBW infants remain poorly understood.

Postnatal dexamethasone administration to ELBW infants has been implicated as a risk factor for FSBP.^{9,10} Three studies have demonstrated significant associations between early postnatal dexamethasone (EPD) and FSBP.^{11,12,14} Two of these were prospective trials evaluating chronic lung disease (CLD) as the primary outcome and FSBP as a secondary outcome,^{12,14} and one was a retrospective study focused on FSBP as the outcome of interest.¹¹ However, two additional large multicenter trials examining EPD for the prevention of CLD failed to find a similar relationship.^{15,16} These discrepant findings could be explained by insufficient sample sizes for this uncommon outcome.

We conducted a systematic literature review to examine the relationship between EPD in ELBW infants and the incidence of FSBP. By combining samples of multiple trials, we hoped to increase the statistical power needed to evaluate FSBP, resolve the current discrepancy, and to estimate the overall risk of FSBP associated with EPD in the ELBW infant. We applied the techniques of meta-analysis to test our hypothesis that ELBW infants who receive EPD have an increased risk for FSBP.

METHODS

Protocol

Prior to data collection, our hypothesis, search strategy, inclusion criteria and analysis strategy were established in accordance with published guidelines for performing a meta-analysis.^{17–19}

Identification of Trials

We identified randomized, placebo-controlled trials of EPD in ELBW infants through searches of Pub Med and Medline electronic data

Departments of Pediatrics (P.V.G., D.D.M.) and Biostatistics (M.L.Y.), University of North Carolina at Chapel Hill, NC.

Address correspondence and reprint requests to Diane D. Marshall, MD MPH, CB# 7596, 4th floor, UNC Hospitals, University of North Carolina, Chapel Hill, NC 27599-7596.



bases using the key word dexamethasone paired with randomized trial, perforation, CLD, bronchopulmonary dysplasia, and low birth weight. In addition, we reviewed abstract indexes from meeting proceedings of the American Academy of Pediatrics and the Society for Pediatric Research during 1997–2000 for the same key words. Similarly, references from identified publications were also reviewed by title. To encompass only the postsurfactant era, all English and non-English publications since 1990 were searched. We accepted studies that were randomized, placebo-controlled trials, administered dexamethasone or placebo within the first 48 hours of life and reported FSBP as an outcome. In addition, we limited our search to studies that enrolled infants with birth weights ≤ 1000 g, or whose study population satisfied the following equation: average birth weight + (standard deviation $\times 2$) ≤ 1000 g (i.e., based on a Gaussian distribution, $\geq 95\%$ of the population with a birth weight ≤ 1000 g). We contacted authors of unpublished trials, informed them of our study, and clarified data discrepancies in one trial.

Data Extraction and Outcome Measures

A data sheet was designed for data collection. The following variables were examined: the year of publication, the study enrollment period, the cumulative 72-hour dose of dexamethasone and the total duration of therapy, the timing of initial dexamethasone dose, the number of infants enrolled in the control and EPD groups, the incidence of FSBP, and the incidence of survival without CLD. We defined CLD as persistent oxygen requirement at 36 weeks' gestational age. Data were extracted independently by two reviewers and compared for agreement. Inconsistencies were resolved with discussion or by contacting the author of the publication in question.

Data and Statistical Methods

We applied chi-square and Fisher's exact tests to determine p -values, odds ratios and 95% confidence intervals (CIs) for FSBP and survival without CLD for each trial. Homogeneity of odds ratios across the studies was assessed using the Breslow-Day test with exact methods. A summary odds ratio of the pooled samples was calculated using the Mantel-Haenszel exact method, stratified by study, for the outcomes

of FSBP and survival without CLD. A p -value of ≤ 0.05 was considered to indicate statistical significance.

Our primary analysis excluded studies that reported a zero incidence of FSBP in both control and dexamethasone treated infants, as their odds ratios could not be calculated and should not contribute to the overall estimate of risk. However, to test the assumption that excluding these study cohorts would not affect our estimate of risk, we repeated the test for homogeneity and summary odds ratio using all studies and substituting 0.5 for the cells with zero incidence.

To assess the quantitative significance of the observed effect size, a number needed to produce one excess effect, NNE, was calculated. This was obtained by taking the reciprocal of the difference in event rates for dexamethasone and control groups, as estimated by a weighted average of such differences for the respective studies.²²

SAS (SAS Institute, Cary NC) and StatXact4 (CYTEL Software Corporation, Cambridge MA) statistical software were used for analyses.

RESULTS

We identified six studies that satisfied our inclusion criteria (Table 1). All were randomized controlled trials evaluating EPD in ELBW infants for the prevention of CLD. Each trial initiated enrollment in 1992 or later. Only one trial, Sinkin et al.,¹⁶ included infants based on gestational age criteria, but met our mean birth weight criteria. The trials by Rastogi et al.²⁰ and Shinwell et al.²¹ included infants up to 1500 and 2000 g, respectively, but reported on subgroups of infants ≤ 1000 g. Dexamethasone was given within 24 hours from birth in five of the six trials, with the duration of study therapy ranging from 1 to 12 days. The timing of FSBP was available only from the study by Garland et al.¹² Our review of reported practice parameters and trial guidelines in each study revealed similar enrollment and exclusion characteristics across the six studies.

The outcome summaries for each of the four trials used for our primary analysis are included in Table 2. Two studies, Rastogi et al.²⁰ and Shinwell et al.,²¹ reported a zero incidence of FSBP in both control and treatment groups and were not included in the primary

Table 1 Search Results for Randomized Placebo-Controlled Trials Investigating EPD in ELBW Infants

Trial (publication date)	<i>N</i>	Enrollment birth weight range (g)	Cumulative 72-hr dexamethasone dose (mg/kg)	Timing of initial dexamethasone dose (hours of age)	Duration of dexamethasone therapy (d)
Shinwell et al. (1995) ²¹	108	500–1000	1.5	<24	3
Rastogi et al. (1996) ²⁰	24	700–999	1.5	<24	12
Garland et al. (1999) ¹²	241	500–1500 (835 \pm 19/825 \pm 19)*	1.35 or 1.175†	24–48	3
Stark et al. (2000) ¹⁴	220	501–1000	0.45	<24	10
Sinkin et al. (2000) ¹⁶	384	<30 weeks' gestation, (890 \pm 19/864 \pm 17)*	1.0	<24	1
Soll (2000) ¹⁵	542	501–1000	1.5	<24	12

*Mean birth weight and standard deviation given for dexamethasone and control groups.

†Dosage was reduced at 25% enrollment after a safety review committee determined the incidence of FSBP was unacceptably high.

Table 2 EPD and the Risk of FSBP and Survival Without CLD

Trial	<i>N</i> EPD	<i>N</i> control	FSBP EPD (%)	FSBP control (%)	Odds ratio (95% CI)	Survival, no CLD EPD (%)	Survival, no CLD control (%)	Odds ratio (95% CI)
Garland et al. ¹²	118	123	12 (10)	7 (6)*	1.86 (0.64, 5.78)	83 (70)	71 (58)	1.74 (0.98, 3.07)†
Stark et al. ¹⁴	111	109	14 (13)	4 (4)	3.79 (1.13, 16.26)	41 (37)	34 (31)	1.29 (0.71, 2.35)
Sinkin et al. ¹⁶	189	195	3 (2)	2 (1)	1.56 (0.18, 18.81)	111 (59)	115 (59)	0.99 (0.65, 1.52)
Soll ¹⁵	271	267	31 (11)	20 (7)	1.60 (0.85, 3.04)	137 (50)‡	124 (47)§	1.16 (0.82, 1.65)
Total	689	694	60 (9)	33 (5)	1.91 (1.21, 3.07)	372 (54)	344 (50)	1.21 (0.97, 1.50)

*One patient with jejunal atresia was excluded from the FSBP analysis.
†Reported relative risk 1.3 (95% CI 1.03, 1.70).
‡Number used for treated = 272.
§Number used for controls = 266.

analysis. Only the trial by Garland et al.¹² reported an association with EPD and survival without CLD (relative risk 1.3, 95% CI 1.03, 1.70; $p=0.03$). The trial by Stark et al.¹⁴ demonstrated an increased risk of FSBP with EPD (odds ratio 3.79, 95% CI 1.13, 16.26; $p=0.03$). Similarly, Garland et al.¹² reported a significant association between EPD and FSBP, but only for perforations occurring in the first week of life ($p=0.009$).

The Breslow-Day test for homogeneity resulted in a p -value of 0.61, indicating that the individual odds ratios were not significantly different and therefore, the four trials were homogenous and combinable. Using this pooled sample of 1383 infants, EPD administration was significantly associated with FSBP (odds ratio 1.91, 95% CI 1.21, 3.07; $p=0.004$). The calculated NNE was 51, indicating one additional FSBP for every 51 ELBW infants treated with EPD.

To determine if the inclusion of the Rastogi et al.²⁰ and Shinwell et al.²¹ trials might alter our findings, we repeated the analysis using all six studies. This yielded a pooled sample of 1518 infants and resulted in findings similar to the initial analysis (odds ratio 1.86, 95% CI 1.19, 2.88; $p=0.004$).

A comparison between the risk of FSBP and survival without CLD was performed using the pooled sample of 1383 infants from our primary analysis. Addressing the outcome of survival without CLD, the Breslow-Day test for homogeneity showed a p -value of 0.42, indicating homogeneity across the four studies. From the pooled sample, a significant association between EPD and survival without CLD was not found (odds ratio 1.21, 95% CI 0.97, 1.50; $p=0.09$).

DISCUSSION

Individual trials of EPD have reported conflicting findings regarding the association between EPD and FSBP. Our analysis, using a pooled sample derived from these randomized controlled trials, estimates a nearly two fold increase in the risk of FSBP in ELBW infants who receive EPD. In contrast, we did not demonstrate an association between EPD and the prevention of CLD. These findings suggest that the risk of FSBP outweighs the benefit of CLD attenuation in ELBW infants.

Our systematic review of the literature identified only six studies for inclusion in our analysis. However, all were rigorous randomized controlled trials designed to measure the effect of EPD on the same primary outcome, CLD. By limiting our search to 1990 or later, we strengthened similarity among practice and diagnostic parameters. These attributes and the statistical homogeneity among the studies support combining them for our analysis.

Our search strategy minimized the potential for publication bias. In addition to studies published in peer-reviewed journals, we abstracted data from a paper in submission¹⁵ and an abstract from a large neonatal network.¹⁶ Also, as most of the trials failed to find an association between EPD and their primary outcome of interest (CLD), it is unlikely that we overlooked negative outcome data. However, we did exclude studies based on their failure to meet our birth weight criteria. Although these studies included infants ≤ 1000 g, we could not abstract outcome data from this subgroup, and consequently excluded the contribution of their data. In addition, the relatively large sample sizes of the individual trials included in our analysis lessen the impact of publication bias.

Methodological differences existed among the included trials and present limitations. First, two studies, Garland et al.¹² and Soll,¹⁵ allowed cross-over patients from untreated to treated status. In the Garland et al study, six of seven infants with FSBP in the control group received rescue dexamethasone therapy before perforation. The Soll study did not provide further information regarding cross-over cases. While differences in the use of intention-to-treat analysis decrease the homogeneity among the studies, the overall result is to blunt our observed effect of EPD on FSBP.

In addition, for the included trials, the initial dose of dexamethasone ranged from 0.15¹⁴ to 0.8 mg/kg per day.¹² A dose-effect of EPD on FSBP is supported by the Garland et al. trial,¹² in which a decrease in the incidence of FSBP was observed after lowering the dexamethasone dose in response to an unacceptably high incidence of FSBP in the first 25% of patients enrolled. However, the trial by Stark et al.¹⁴ used the smallest dexamethasone dose among the studies, but still demonstrated a significant association with FSBP. In addition, our test of homogeneity suggests that a dose-effect did not alter our observed estimate of effect.

Similarly, variation in the duration of dexamethasone therapy existed among the included trials. Sinkin et al.¹⁶ suggests that their low incidence of FSBP in treated infants, 2% vs. 10% to 13% for the other trials, might reflect their shorter duration of EPD therapy, 1 day vs. 3 to 12 days. However, their incidence of FSBP was also low in the control group relative to the other trials, 1% vs. 4% to 7%. This suggests a difference in a population or practice characteristic among the infants in the Sinkin et al trial or could reflect reporting differences.

An association between EPD and FSBP could also be affected by the timing of FSBP diagnosis. For example, the trial by Garland et al.¹² found an increase in the risk of FSBP associated with EPD only for FSBPs occurring in the first week of life. Information regarding the timing of FSBP was unavailable for the remaining studies. It is possible that late occurring perforations, not causally related to EPD, were included, inflating the observed estimate of effect.

Biases inherent in the reporting of FSBP limited our analysis. Studies were most commonly excluded from our analysis for failure to report FSBP as an outcome. Likewise, diagnostic criteria for FSBP were lacking for most studies. All studies that reported FSBP also reported an incidence of necrotizing enterocolitis. The studies by Garland et al.¹² and Soll¹⁵ offered a definition of FSBP, using radiographic criterion, and the Stark et al.¹⁴ study clarified the absence of necrotizing enterocolitis with spontaneous perforation. Due to similarities in their clinical presentation, underreporting of FSBP and overreporting of necrotizing enterocolitis may occur.¹¹ Although this could result in an underestimation of the incidence of FSBP, this misclassification should affect both treatment and control groups equally, but might blunt the observed magnitude of the effect of EPD.

The etiology of FSBP remains poorly defined and multiple risk factors may play a role. Both human and animal studies have demonstrated an effect of dexamethasone on ileal development.^{11,23} Dexamethasone increases mucosal maturation, but disrupts growth of the surrounding smooth muscle, potentiating structural weakness in the bowel wall.^{11,23} The dilatory stresses associated with rapid growth and secretory function of the distal small intestine may also increase susceptibility to ileal perforation in the ELBW infant. Likewise, other processes or medications that affect ileal development could also increase the risk for FSBP. Specifically, indomethacin has been associated with intestinal perforation in animal studies,²⁴ and has been identified as a confounder of the observed effect of EPD in human trials.¹⁴ Information regarding the use of indomethacin, as well as antenatal steroids, was not available for all of the trials included in our analysis. However, the use of indomethacin for prophylaxis of intracranial hemorrhage, and antenatal steroids for the prevention of respiratory distress syndrome were accepted practices during each of the study periods, and therefore, they represent potential confounders.

To express the magnitude of the difference in risk of FSBP among treated and control groups, we calculated an NNE of 51. This

estimate of the number needed to treat to incur one additional effect is based, in part, on the variance in each individual trial. As a result, the study by Sinkin et al.,¹⁶ which demonstrated the smallest variance in effect, had a greater influence and resulted in an increase in magnitude of the NNE. Excluding the Sinkin study, results in an NNE of 19. The overall low incidence of FSBP in the Sinkin et al.¹⁶ study has not been explained, and the true NNE for EPD and FSBP may be much smaller than 51.

Dexamethasone has been widely used for the treatment of CLD in preterm infants and its early use for the prevention of CLD has been tested in multiple trials. The efficacy of EPD in preventing CLD is controversial, and although our study was not aimed at exploring this issue, we failed to find an association in the ELBW population. Recent literature suggests a number of adverse effects with the use of dexamethasone in preterm infants, including abnormal growth and neurodevelopmental outcome.^{25,26} Our analysis supports an association between EPD and another adverse outcome, FSBP. Consequently, we support the discontinuation of EPD as a prophylactic therapy in ELBW infants, and suggest alternative therapies, such as the use of hydrocortisone, be further explored.

Acknowledgments

We are indebted to Sandra Woolson and Gary Koch, PhD, from the Department of Biostatistics at The University of North Carolina at Chapel Hill for their technical assistance and to Carl Bose, MD, and Sarabeth Thomas, MS, for review of our manuscript.

References

1. Buecheit JQ, Stewart DL. Clinical comparison of localized intestinal perforation and necrotizing enterocolitis in neonates. *Pediatrics* 1994;93:32–6.
2. Novack CM, Waffrin F, Sills JH, Pousti TJ, Warden JM, Cunningham MD. Focal intestinal perforation in the extremely-low-birth-weight infant. *J Perinatol* 1994;XIV:450–3.
3. Raghuvveer G, Speidel B, Marlow N, Porter H. Focal intestinal perforation in preterm infants is an emerging disease. *Acta Paediatr* 1996;85:237–9.
4. Kuhl G, Wille L, Bolkonius M, Seyberth HW. Intestinal perforation associated with indomethacin treatment in premature infants. *Eur J Pediatr* 1985; 143:213.
5. McDonnell M, Evans N. Upper and lower gastrointestinal complications with dexamethasone despite H2 antagonists. *J Paediatr Child Health* 1995;31: 152–4.
6. Ng PC, Fok TF, So KW, Wong W, Yip PKF. Lower gastrointestinal tract perforation in preterm infants treated with dexamethasone for bronchopulmonary dysplasia. *Pediatr Surg Int* 1997;12:211–2.
7. Alpan G, Eyal F, Vinograd I, Udassin R, Amir G, Mogle P, Glick B. Localized intestinal perforation after enteral administration of indomethacin in premature infants. *J Pediatr* 1985;106:277.
8. Loyd JR. The etiology of gastrointestinal perforations in the newborn. *J Pediatr Surg* 1969;4:77.
9. McCarthy DW, Qualman S, Besner GE. Absent intestinal musculature: anatomic evidence of an embryonic origin of the lesion. *J Pediatr Surg* 1994;29:1476–8.

10. Liwin A, Avidor I, Schujman E, Grunebaum M, Wilunsky E, Wollock Y, reisner SH. Neonatal intestinal perforation caused by congenital defects of the intestinal musculature. *Am J clin Pathol* 1984;81:77–80.
11. Gordon P, Rutledge J, Sawin R, Thomas S, Woodrum D. Early postnatal dexamethasone increases the risk of focal small bowel perforation in extremely low birth weight infants. *J. Perinatol* 1999;19 (8 Pt 1):573–77.
12. Garland J, Colleen A, Thomas P, Whitehead V, Brand J, Winston J, Samuels D, McAuliffe T. A three-day course of dexamethasone therapy to prevent chronic lung disease in ventilated neonates: a randomized trial. *Pediatrics* 1999;104 (1):91–9.
13. Aschner JL, Deluga KS, Metlay LA, Emmens RW, Hendricks-Munoz KD. Spontaneous focal gastrointestinal perforation in very low birth weight infants. *J Pediatr* 1988;113:364–7.
14. Stark A, Waldemar C, Bauer C, Donovan E, Oh W, Papile L, Shankran S, Tyson J, Wright L, Saha S, Poole K. Serious complications in a randomized trial of early stress dose dexamethasone (DEX) in extremely low birth weight (ELBW) infants. *Pediatr Res* 47 (4):434A.
15. Soll R. Early postnatal dexamethasone therapy for the prevention of chronic lung disease. *N Engl J Med* 2000. [In press].
16. Sinkin R, Harry D, Horgan M, Gallaher K, Cox C, Maniscalco W, Chess P, D'Angio C, Guillet R, Kendig J, Ryan R, Phelps D. Early dexamethasone-attempting to prevent chronic lung disease. *Pediatrics* 2000;105 (3):542–48.
17. L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med* 1987;107 (2):224–33.
18. Cook D, Sackett D, Spitzer W. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam consultation on meta-analysis. *J Clin Epidemiol* 1995;48:167–71.
19. Sacks HS, Reitman D, Pagano D, Kupelnick B. Meta-analysis: an update. *Mt Sinai J Med* 1996;63 (3–4):216–24.
20. Rastogi A, Akintorin S, Bez M, Morales P, Pildes R. A controlled trial of dexamethasone to prevent bronchopulmonary dysplasia in surfactant-treated infants. *Pediatrics* 1996;98 (2):204–10.
21. Shinwell E, Karplus M, Zmora E, Reich D, Rothschild A, Blazer S, Bader D, Yurman S, Dolfin F, Kuint J, Milbauer B, Kohelet D, Goldberg M, Armon Y, Davidson S, Sirota L, Amitai M, Zaretsky A, Barak M, Gattfried S. Failure of early postnatal dexamethasone to prevent chronic lung disease in infants with respiratory distress syndrome. *Arch Dis Child* 1996;74:F33–37.
22. Feinstein AR. Indexes of contrast and quantitative significance for comparisons of two groups. *Stat Med* 1999;18:2557–81.
23. Gordon P, Price W, Stiles A. Dexamethasone administration to newborn mice alters mucosal and muscular morphology in the ileum and modulates insulin-like growth factor (IGF) I localization. *Pediatr Res* 2000. [In press, manuscript # 00-104092].
24. Nygard G, Anthony A, Piasecki C, Trevethick MA, Hudson M, Dhillon AP, Pounder RE, Wakefield AJ. Acute indomethacin-induced injury in the rat; early morphologic and biochemical changes. *Gastroenterology* 1994;106:567–75.
25. Yeh TF, Lin YJ, Huang CC, Chen YJ, LINCH, Lin HC, Hsieh W, Lien YJ. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics* 1998;101 (5)E7.
26. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG, Dillard RG. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. *Pediatrics* 1999 Jul;104 (1 Pt 1):15–21.