Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation

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ABSTRACT

BACKGROUND

Perforated necrotizing enterocolitis is a major cause of morbidity and mortality in premature infants, and the optimal treatment is uncertain. We designed this multicenter randomized trial to compare outcomes of primary peritoneal drainage with laparotomy and bowel resection in preterm infants with perforated necrotizing enterocolitis.

METHODS

We randomly assigned 117 preterm infants (delivered before 34 weeks of gestation) with birth weights less than 1500 g and perforated necrotizing enterocolitis at 15 pediatric centers to undergo primary peritoneal drainage or laparotomy with bowel resection. Postoperative care was standardized. The primary outcome was survival at 90 days postoperatively. Secondary outcomes included dependence on parenteral nutrition 90 days postoperatively and length of hospital stay.

RESULTS

At 90 days postoperatively, 19 of 55 infants assigned to primary peritoneal drainage had died (34.5 percent), as compared with 22 of 62 infants assigned to laparotomy (35.5 percent, P=0.92). The percentages of infants who depended on total parenteral nutrition were 17 of 36 (47.2 percent) in the peritoneal-drainage group and 16 of 40 (40.0 percent) in the laparotomy group (P=0.53). The mean (±SD) length of hospitalization for the 76 infants who were alive 90 days after operation was similar in the primary peritoneal-drainage and laparotomy groups (126±58 days and 116±56 days, respectively; P=0.43). Subgroup analyses stratified according to the presence or absence of radiographic evidence of extensive necrotizing enterocolitis (pneumatosis intestinalis), gestational age of less than 25 weeks, and serum pH less than 7.30 at presentation showed no significant advantage of either treatment in any group.

CONCLUSIONS

The type of operation performed for perforated necrotizing enterocolitis does not influence survival or other clinically important early outcomes in preterm infants. (ClinicalTrials.gov number, NCT00252681.)

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NECROTIZING ENTEROCOLITIS IS A SEvere inflammatory disorder of the intestine occurring in premature infants. It is a major cause of death and morbidity in neonates.[1] In contrast to the improvements during the past 30 years in the outcomes of many conditions affecting premature infants, the mortality rate of 30 to 50 percent for babies with intestinal perforation due to necrotizing enterocolitis remains essentially unchanged.[2]

The standard approach to patients with perforated intestine, necrotic intestine, or both is surgical resection of the involved bowel with the creation of intestinal stomas. In a critically ill premature infant, this entails substantial risks. Primary peritoneal drainage, a minimally invasive operation, has evolved as an alternative.[3] It involves a small abdominal incision with placement of a drain into the peritoneal cavity without a formal laparotomy or bowel resection.

There is considerable controversy regarding which procedure is preferable. Evidence consists largely of case series from single institutions.[4] Currently, in the absence of rigorous evidence supporting the superiority of one approach over the other, the care of infants requiring surgical intervention depends mostly on the local biases of the treating institution or the individual surgeon.

We conducted a multicenter, randomized clinical trial to determine whether primary peritoneal drainage improves survival 90 days postoperatively as compared with laparotomy and resection for very-low-birth-weight (less than 1500 g) premature infants with perforated necrotizing enterocolitis. We also assessed whether primary peritoneal drainage, as compared with laparotomy and resection, reduced the frequency of dependence on total parenteral nutrition 90 days after operation or reduced the length of hospital stay in surviving infants.

METHODS

PATIENTS

We conducted this multicenter, randomized, controlled clinical trial in 15 newborn intensive care units (NICUs) in the United States and Canada with the approval of the institutional review board at each site. We limited eligibility to preterm infants (birth weight, <1500 g; gestational age, <34 weeks) with evidence of intestinal perforation, in-

cluding free intraperitoneal air on an abdominal radiograph (96 infants); stool, bile, or pus found at paracentesis (5); or clinical evidence of perforation in the joint opinion of the attending surgeon and the neonatologist (16). This definition included both infants with extensive disease and others with focal perforation. Infants with gastrointestinal anomalies, a previous abdominal operation, or bilateral grade IV intraventricular hemorrhage (i.e., severe intraventricular hemorrhage) were not eligible.

STUDY PROTOCOL

The families of the patients were counseled and asked by the attending pediatric surgeon to provide written informed consent. Enrolled infants were randomly assigned to either peritoneal drainage or laparotomy within permuted blocks of four, with block size unknown to the investigators. Randomization was stratified according to birth weight (<1000 g vs. 1000 to 1499 g). Random allocation sequence was maintained by means of sequentially numbered, sealed envelopes for each stratum. To ensure that clinical care was uniform in the two groups, all infants were entered into a standardized critical pathway directing their preoperative and postoperative care.

TREATMENT

Laparotomy

Patients randomly assigned to laparotomy underwent abdominal exploration through a transverse abdominal incision. All frankly necrotic intestine was resected. Intestinal stomas were created in the location selected by the attending surgeon. Where feasible, the stoma was created proximal to the active disease. If evidence of further intestinal necrosis or perforation developed, patients underwent additional laparotomies.

Primary Peritoneal Drainage

Patients randomly assigned to primary peritoneal drainage received a 1/4-in. (0.6-cm), full-thickness incision in the right lower quadrant of the abdomen. Stool and pus were expressed manually from the peritoneal cavity, which was then irrigated with warmed saline solution until clear. A long, 1/4-in. Penrose drain was placed by means of the incision in the right lower quadrant and routed to all quadrants of the abdomen. A second drain was placed if the surgeon believed it was needed to provide effective drainage. If the peritoneal cav-

ity was believed to be inadequately drained, on the basis of the reaccumulation of air or fluid in the abdomen, the original drain was manipulated or an additional drain was placed to establish effective peritoneal drainage.

Previous data indicated that the condition of patients surviving after peritoneal drainage often deteriorates before it improves and that performing "salvage laparotomy" after peritoneal drainage does not improve the outcome.[5,6] The protocol allowed for but did not encourage early laparotomy in patients with persistent metabolic acidosis, hemodynamic instability, and respiratory failure. Patients in the primary-peritoneal-drainage group who survived the initial episode of necrotizing enterocolitis but in whom stricture or bowel obstruction developed underwent delayed corrective laparotomy and were analyzed in the primary-peritoneal-drainage group.

OUTCOME MEASURES

The primary outcome measure was mortality 90 days after the intervention. Secondary outcome measures were dependence on total parenteral nutrition 90 days postoperatively and the length of hospital stay for patients surviving 90 days postoperatively.

DATA COLLECTION AND MANAGEMENT

Demographic information was collected on all enrolled patients, as were medical histories and clinical data, including a detailed daily assessment of the status of feeding, respiration, and infections. Similar data were collected for all infants who were eligible but not enrolled. The operating surgeon determined the surgical intervention for all nonenrolled patients. Survival data 90 days after intervention were collected for all patients. Data were transmitted to the Yale Center for Children's Surgical Research, where quality-control procedures were implemented and data were entered into a database for analysis.

DATA AND SAFETY MONITORING

An independent data and safety monitoring board was established to monitor mortality and patient safety during the study and to examine interim results for the primary outcome variable after the treatment of 69 patients (approximately half the number required for study completion). The chi-square stopping boundary according to the Pocock method of analysis, with an alpha level of 0.05 and a statistical power of 80 percent, was not exceeded at the interim analysis.

STATISTICAL ANALYSIS

The trial was designed to enroll 130 patients in order to have a statistical power of 82 percent to detect a reduction in the risk of death from 50 to 25 percent among patients undergoing peritoneal drainage as compared with laparotomy. A P value of less than 0.05 was considered to indicate statistical significance, and all tests were two-sided. Enrollment was closed after 117 patients because funding ended. We used the log-rank test and Cox proportional-hazards regression, adjusting for birth weight, sex, presence or absence of pneumatosis, presence or absence of ventilator dependence, and platelet count on survival, to compare Kaplan–Meier survival curves for the two treatment groups and to evaluate mortality 90 days postoperatively. The primary outcome variable was also measured as mortality 90 days post-
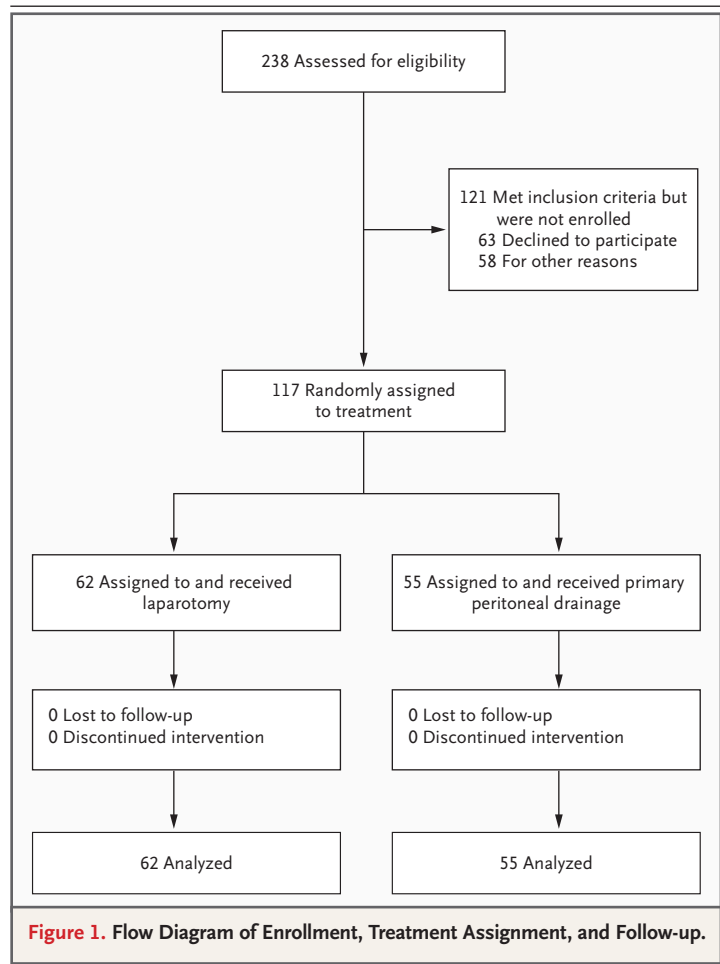

Figure 1. Flow Diagram of Enrollment, Treatment Assignment, and Follow-up.

Table 1. Baseline Characteristics of the 117 Patients.*

Characteristic	Laparotomy (N = 62)	Primary Peritoneal Drainage (N = 55)	Total (N = 117)	P Value
Male sex — no. (%)	42 (67.7)	30 (54.5)	72 (61.5)	0.14
Race or ethnic group — no. (%)				0.07†
White	23 (37.1)	15 (27.3)	38 (32.5)	
Black	21 (33.9)	21 (38.2)	42 (35.9)	
Native American	7 (11.3)	14 (25.5)	21 (17.9)	
Asian	5 (8.1)	0	5 (4.3)	
Unknown	6 (9.7)	5 (9.1)	11 (9.4)	
Hispanic ethnic background — no. (%)				0.82
Yes	4 (6.5)	3 (5.5)	7 (6.0)	
No	58 (93.5)	52 (94.5)	110 (94.0)	
Birth weight — g	878±251	835±276	—	0.38
Birth weight — no. (%)				0.24
<1000 g	45 (72.6)	45 (81.8)	90 (76.9)	
≥1000 g	17 (27.4)	10 (18.2)	27 (23.1)	
Gestational age — wk	26.2±2.1	25.8±2.1	—	0.29
Gestational age — no. (%)				0.39†
≤24 wk	14 (22.6)	15 (27.3)	29 (24.8)	
25 to 26 wk	23 (37.1)	26 (47.3)	49 (41.9)	
27 to 30 wk	19 (30.6)	10 (18.2)	29 (24.8)	
>30 wk	6 (9.7)	4 (7.3)	10 (8.5)	
Age at operation — days	13.8±12.8	13.5±10.2	—	0.88
Age at operation — no. (%)				0.14†
≤5 days	8 (12.9)	13 (23.6)	21 (18.0)	
6 to 10 days	29 (46.8)	16 (29.1)	45 (38.5)	
11 to 20 days	14 (22.6)	14 (25.5)	28 (23.9)	
21 to 45 days	9 (14.5)	12 (21.8)	21 (18.0)	
>45 days	2 (3.2)	0	2 (1.7)	
One-minute Apgar score — no. (%)				0.99†
≤3	21 (33.9)	19 (34.5)	40 (34.2)	
4 to 6	21 (33.9)	19 (34.5)	40 (34.2)	
>6	20 (32.2)	17 (30.9)	37 (31.6)	
Five-minute Apgar score — no. (%)				0.24†
≤5	16 (25.8)	10 (18.2)	26 (22.2)	
6 to 7	15 (24.2)	21 (38.2)	36 (30.8)	
>7	31 (50.0)	24 (43.6)	55 (47.0)	

operatively with the use of the chi-square statistic (power of 85 percent with 117 patients). The secondary outcome variables were the presence or absence of the need for parenteral nutritional support on the 90th postoperative day and length of hospital stay. The differences in these variables were compared, first with the use of contingency tables and chi-square tests of significance, and then by estimation of the relative risk between treatment groups. Prespecified sub-

Table 1. (Continued.)

Characteristic	Laparotomy (N = 62)	Primary Peritoneal Drainage (N = 55)	Total (N = 117)	P Value
Clinical characteristic before evidence of intestinal perforation				
Enteral feeding — no./total no. (%)	41/61 (67.2)	40/54 (74.0)	81/115 (70.0)	0.42
No. of days of preoperative enteral feeding‡	9.78±11.1	8.36±7.9	—	0.51
Weight — g§	928±294	918±301	—	0.86
pH¶	7.26±0.11	7.28 ± 0.92	—	0.31
Age at operation — days	13.8±12.8	13.5±10.2	—	0.88
Pneumatosis on radiography — no./total no. (%)	21/59 (35.6)	23/52 (44.2)	44/111 (39.6)	0.35
Required mechanical ventilation — no./total no. (%)	50/62 (80.6)	48/55 (87.3)	98/117 (83.8)	0.33
Patent ductus arteriosus — no./total no. (%)	28/61 (45.9)	20/55 (36.4)	48/116 (41.4)	0.30
Intraventricular hemorrhage — no./total no. (%)‖	27/51 (52.9)	22/42 (52.3)	49/93 (52.7)	0.96
Received corticosteroids — no./total no. (%)	15/62 (24.2)	18/54 (33.3)	33/116 (28.4)	0.28
Received indomethacin — no./total no. (%)	29/62 (46.8)	22/55 (40.1)	51/117 (43.6)	0.51
Received vasopressors — no./total no. (%)	31/59 (52.5)	27/52 (51.9)	58/111 (52.3)	0.95
Received antibiotics — no./total no. (%)	55/62 (88.7)	49/55 (89.1)	104/117 (88.9)	0.95
Positive blood culture — no./total no. (%)	10/40 (25.0)	8/36 (22.2)	18/76 (23.7)	0.77
Platelet count — $\times10^{-3}/mm^3$**	190.3±105.9	171.7±127.8	—	0.43
White-cell count — $\times10^{-3}/mm^3$**	17.2±16.3	13.8±20.4	—	0.28

* Plus–minus values are means ±SD. Dashes denote not applicable. Race or ethnic group was assigned by the investigators.
† The P value was by analysis of variance for all groups. Data were missing for 37 patients.
‡ The P value was by analysis of variance for all groups. Data were missing for one patient.
§ The P value was by analysis of variance for all groups. Data were missing for nine patients.
¶ The P value was by analysis of variance for all groups.
‖ Intraventricular hemorrhage was determined with the use of cranial ultrasonography.
** Data were missing for 15 patients.

group analysis was performed on groups stratified according to gestational age (<25 weeks vs. ≥25 weeks), serum pH (<7.30 vs. ≥7.30), and the presence or absence of pneumatosis on radiographs.

RESULTS

PATIENTS

Between July 1999 and May 2005, 117 neonates with perforated necrotizing enterocolitis were randomly assigned to laparotomy or primary peritoneal drainage (Fig. 1). One hundred twenty-one other patients were eligible for the trial but were not enrolled, 63 (52.1 percent) owing to family refusal, 30 (24.8 percent) because the surgeon did not offer enrollment, 14 (11.6 percent) because the parents were not available to provide consent, and 14 (11.6 percent) for other reasons. All enrolled patients received the assigned treatment and were entered into the critical pathway for postoperative care. Five patients in the peritoneal-drainage group subsequently underwent laparotomy for clinical deterioration.

The baseline characteristics and clinical status of the two groups were similar (Table 1), including birth weight, history of enteral feeding, pH, platelet count, and other potential predictors of survival and disease severity in perforated necrotizing enterocolitis. Of patients who were eligible but did not enroll, the baseline characteristics and mortality after 90 days were similar to those

of the study patients, suggesting that the study population reasonably represented the spectrum of neonates with necrotizing enterocolitis in the institutions that provided treatment (Table 2).

OUTCOMES

The primary outcome variable — mortality 90 days after operation — was not significantly different between the primary-peritoneal-drainage group and the laparotomy group (34.5 percent and 35.5 percent, respectively; P=0.92; relative risk associated with laparotomy, 1.03; 95 percent confidence interval, 0.63 to 1.69) (Table 3 and Fig. 2). There were also no significant differences between the primary-peritoneal-drainage group and the laparotomy group in the rates of dependence on

parenteral nutrition 90 days after surgery or in the mean duration of hospital stay for the 76 patients surviving at least 90 days postoperatively (126±58 days and 116±56 days, respectively; P=0.43).

With the use of Cox proportional-hazards regression, we found no significant associations between mortality and the following variables: birth weight, the presence or absence of pneumatosis intestinalis, ventilator status, platelet count, and sex. However, power was limited in multivariate analyses to detect such associations.

Five patients in the primary-peritoneal-drainage group underwent laparotomy for clinical deterioration between day 2 and day 45 postoperatively, and one died. Sixteen patients in the peritoneal-drainage group underwent delayed laparotomy for

Table 2. Comparison of Enrolled Patients and Eligible but Nonenrolled Patients Who Had Perforated Necrotizing Enterocolitis.*

Variable	Enrolled Patients (N=117)	Eligible Nonenrolled Patients (N=121)	P Value	Eligible Nonenrolled Patients Who Underwent Laparotomy (N=48)	Eligible Nonenrolled Patients Who Underwent Primary Peritoneal Drainage (N=73)	P Value
Male sex — no. (%)	72 (61.5)	78 (64.5)	0.64	30 (62.5)	48 (65.8)	0.72
Race or ethnic group — no. (%)†			0.03‡			0.49‡
White	38 (32.5)	52 (43.0)		22 (45.8)	30 (41.1)	
Black	42 (35.9)	50 (41.3)		21 (43.8)	29 (39.7)	
Native American	21 (17.9)	7 (5.8)		3 (6.2)	4 (5.5)	
Asian	5 (4.3)	3 (2.5)		0	3 (4.1)	
Unknown	11 (9.4)	9 (7.4)		2 (4.2)	7 (9.6)	
Hispanic ethnic background — no. (%)	7 (6.0)	3 (2.5)	0.73	1 (2.1)	2 (2.7)	0.95
Birth weight — g	857±263	831±242	0.43	931±240	766±221	<0.001
Birth weight — no. (%)			0.99			0.009
<1000 g	90 (76.9)	93 (76.9)		31 (64.6)	62 (84.9)	
≥1000 g	27 (23.1)	28 (23.1)		17 (35.4)	11 (15.1)	
Gestational age — wk	27.8±2.5	27.8±2.4	0.96	26.8±2.1	25.5±2.0	<0.001
Gestational age — no. (%)			0.53‡			0.007‡
≤24 wk	29 (24.8)	37 (30.6)		7 (14.6)	30 (41.1)	
25 to 26 wk	49 (41.9)	40 (33.1)		17 (35.4)	23 (31.5)	
27 to 30 wk	29 (24.8)	34 (28.1)		17 (35.4)	17 (23.3)	
>30 wk	10 (8.5)	10 (8.3)		7 (14.6)	3 (4.1)	
Age at operation — days	13.6±11.6	15.2±12.0	0.32	15.8±13.5	14.7±11.0	0.64
Death within 90 days after intervention — no./total no. (%)	41/117 (35.0)	36/117 (30.8)	0.49	7/47 (14.9)	29/70 (41.4)	0.002

* Plus–minus values are means ±SD.
† Race or ethnic group was determined by the research team.
‡ The P value was by analysis of variance.

stricture, bowel obstruction, or intolerance of enteral feeding between day 26 and day 180 postoperatively, and two died. All patients randomly assigned to primary peritoneal drainage who received early or delayed laparotomy were analyzed in the peritoneal drainage group.

Analyses stratified according to birth weight and those stratified according to the presence or absence of pneumatosis on abdominal radiographs showed no significant benefit of either treatment (Table 3). Because drainage has been suggested by some to benefit only the smallest infants in the least stable condition, we also performed prespecified subgroup analyses of infants at a gestational age of less than 25 weeks and with a serum pH below 7.30. In terms of the treatment, we found no significant difference in mortality at 90 days after surgery or dependence on total parenteral nutrition. However, the subgroup analyses were limited by small numbers. We also found no significant differences in results according to the four study sites that enrolled more than 10 patients.

DISCUSSION

Among low-birth-weight infants who have intestinal perforation considered to be caused by nec-

Table 3. Mortality and Dependence on Total Parenteral Nutrition 90 Days after Intervention for Surviving Infants in Relation to Other Clinical Characteristics.

Variable	Laparotomy	Primary Peritoneal Drainage	P Value	Relative Risk (95% CI)*
	number/total number (percent)			
Mortality				
All patients	22/62 (35.5)	19/55 (34.5)	0.92	1.03 (0.63–1.69)
<1000 g	15/45 (33.3)	16/45 (35.6)	0.82	0.94 (0.53–1.66)
≥1000 g	7/17 (41.2)	3/10 (30)	0.56	1.37 (0.46–4.14)
Pneumatosis on radiography	11/21 (52.4)	9/23 (39.1)	0.38	1.34 (0.70--2.57)
No pneumatosis on radiography	11/38 (28.9)	9/29 (31.0)	0.85	0.93 (0.45–1.95)
Gestational age				
<25 wk	9/30 (30.0)	10/31 (32.3)	0.85	0.93 (0.44–1.96)
≥25 wk	13/32 (40.6)	9/24 (37.5)	1.00†	1.08 (0.56–2.11)
pH				
<7.30	17/37 (45.9)	11/34 (32.4)	0.24	1.42 (0.78–2.58)
≥7.30	5/25 (20.0)	8/21 (38.1)	0.20†	0.53 (0.20–1.36)
Dependence on total parenteral nutrition 90 days after intervention				
All patients	16/40 (40.0)	17/36 (47.2)	0.53	0.85 (0.51–1.42)
<1000 g	12/30 (40.0)	15/29 (51.7)	0.37	0.77 (0.44–1.36)
≥1000 g	4/10 (40.0)	2/7 (28.6)	1.00†	1.40 (0.35–5.65)
Pneumatosis on radiography	6/10 (60.0)	9/14 (64.3)	1.00†	0.93 (0.49–1.77)
No pneumatosis on radiography	10/27 (37.0)	8/20 (40.0)	0.84	0.93 (0.45–1.92)
Gestational age				
<25 wk	8/21 (38.1)	9/21 (42.9)	0.75	0.89 (0.43–1.85)
≥25 wk	8/19 (42.1)	8/15 (53.3)	0.73†	0.79 (0.39–1.60)
pH				
<7.30	8/20 (40.0)	10/23 (43.5)	0.82	0.92 (0.45–1.87)
≥7.30	8/20 (40.0)	7/13 (53.8)	0.49†	0.74 (0.36–1.55)

* The relative risk is reported as the risk of an event with laparotomy as compared with the risk of an event with peritoneal drainage. CI denotes confidence interval.
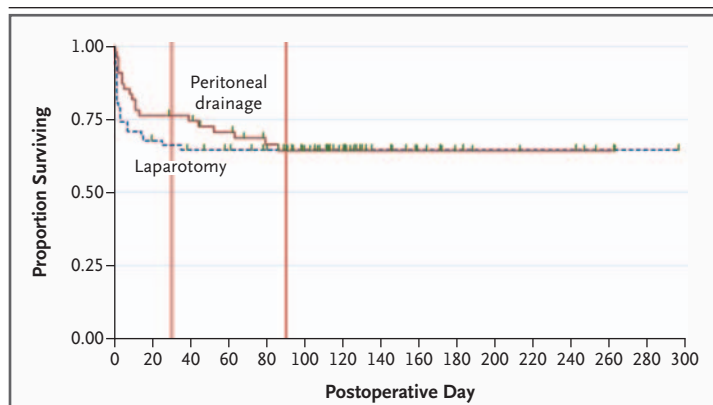† The P value was determined with Fisher's exact test.

Figure 2. Kaplan–Meier Survival Curves for the Laparotomy Group and the Peritoneal-Drainage Group.

Survival curves were compared with the use of the log-rank test ($\chi^2=0.19$) and Cox proportional-hazards regression (0.66), adjusting for birth weight, sex, presence or absence of pneumatosis, presence or absence of ventilator dependence, and platelet count.

rotizing enterocolitis, we found no significant differences in mortality among those who underwent laparotomy and bowel resection as compared with those who underwent primary peritoneal drainage. We also found no significant differences between groups in the dependence on parenteral nutrition 90 days after operation or in the duration of hospital stay in surviving infants.

Primary peritoneal drainage was first attempted in 1976 as a possible treatment for intestinal perforation in the smallest preterm infants in the least stable condition.[3] At the time, the condition of this group of patients was believed to be too unstable to tolerate laparotomy, which was the conventional approach. Several anecdotal reports suggested that peritoneal drainage resulted in the unexpected survival of these infants.[7,8] Subsequently, some retrospective observational case series reported survival rates with drainage approaching or exceeding those with laparotomy, whereas others suggested that laparotomy was the superior treatment.[9-14]

Some of the authors of the present study reviewed 475 published cases and 190 unpublished cases of patients who underwent either laparotomy and resection or primary peritoneal drainage. They concluded that selection bias and the inability to determine what factors influenced the treatment assignment precluded meaningful comparisons of these approaches.[15] In previous observational studies, peritoneal drainage was used in smaller babies in unstable condition because of

the beliefs that these babies may not tolerate laparotomy and may have better outcomes after peritoneal drainage. The findings of our study refute those beliefs. Our results in larger babies are limited by small numbers but do not suggest that, because these babies can "tolerate" laparotomy, it is the best treatment.

In some cases, peritoneal drainage has been used as a temporizing procedure, followed by laparotomy in two to three days. Previous observational studies have suggested that mortality with this approach is higher than with either primary peritoneal drainage or laparotomy alone.[5] The condition of patients undergoing peritoneal drainage often improves slowly. Examination of the clinical status for the first several days after peritoneal drainage of patients who ultimately survive, as compared with those who do not, has shown no discernible differences.[5] This suggests that there is no reliable means to determine which patients are destined to do poorly after primary peritoneal drainage and might be candidates for "salvage" laparotomy.

Several investigators have suggested that the choice of operation in patients with perforated necrotizing enterocolitis should be made on the basis of the presenting radiographic findings.[16] They argue that patients with free intraperitoneal air in the absence of pneumatosis are most likely to have necrotizing enterocolitis of only a short segment of the intestine or isolated intestinal perforation and are best treated with primary peritoneal drainage.[17-19] In contrast, patients with pneumatosis may have more extensive intestinal involvement and may benefit from laparotomy and bowel resection. Previous observational data from a large, multicenter study, however, suggested that survival among patients without pneumatosis was not greater with peritoneal drainage than with laparotomy.[20] Our subgroup analysis, although limited by small numbers, also did not show a benefit of primary peritoneal drainage over laparotomy in infants without pneumatosis (i.e., with more limited disease) or of laparotomy over primary peritoneal drainage in infants with pneumatosis (i.e., more extensive disease).

Our study had some limitations. The size of the study group was chosen to have a statistical power of more than 80 percent to detect a lowering of the mortality rate from 50 to 25 percent. Because the ultimate sample size was smaller than

originally planned, the actual power to detect differences of this magnitude was 77 percent. Clinical effects smaller than this are more likely to have been missed. We found no significant reduction in the risk of mortality after primary peritoneal drainage as compared with laparotomy (relative risk, 1.03; 95 percent confidence interval, 0.63 to 1.69), but we cannot exclude the possibility of clinically important reductions or increases in mortality with one approach or the other.

In addition, we studied only short-term outcomes of the interventions. Several reports have shown significant neurodevelopmental impairment of many survivors of necrotizing enterocolitis,[21-24] and the effect of laparotomy as compared with primary peritoneal drainage on these outcomes is unknown.[25] A multicenter observational study has suggested a possible trend toward a better neurodevelopmental outcome with laparotomy than with drainage.[26] Longer follow-up is required to assess whether there are neurodevelopmental differences between the groups.

Many infants were not enrolled in the study, and it is possible that differences between patients who were eligible for the trial and those who actually enrolled could have influenced the results. However, a detailed analysis of eligible nonenrolled patients suggests that they were similar to enrolled patients. Furthermore, among nonenrolled patients (for whom the decision regarding the type of operation reflected the preference of the surgeon), laparotomy and primary peritoneal drainage were used in widely disparate patient groups. Unlike in the randomized trial, the infants who underwent laparotomy had better outcomes. This observation underscores the susceptibility of nonrandomized studies of the outcomes of these operations to selection bias and confounding bias.

Our results do not address the question of whether patients with perforated necrotizing enterocolitis benefit from having any surgical intervention. The current findings suggest that once necrotizing enterocolitis has progressed to perforation, the type of surgical intervention is not a significant determinant of outcome. These results point to the need for research on approaches to better identify subgroups of premature infants at risk for intestinal perforation and on interventions to reduce morbidity and mortality in these infants. Invasive surgical therapy does not necessarily improve outcome. In fetal surgery, dramatic technical successes led to nonrandomized reports of the efficacy of open fetal repair and tracheal occlusion in improving the outcome among infants with congenital diaphragmatic hernia. Subsequent randomized trials found these therapies to be no more effective than standard postnatal care.[27,28]

Our data suggest that the type of operation performed for intestinal perforation in infants with necrotizing enterocolitis does not significantly affect mortality, the dependence on total parenteral nutrition, or the length of hospital stay. Our results also underscore the importance of randomized, controlled trials in evaluating surgical therapies.

APPENDIX

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