Surgical Management of Bowel Perforations and Outcome in Very Low-Birth-Weight Infants (≤1,200 g)

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Purpose: The efficacy of peritoneal drainage (PD) as an alternative to laparotomy (LAP) in the management of bowel perforation (PRF) in very low-birth-weight infants (VLBW ≤ 1,200 g) remains uncertain. The authors hypothesized that survival of VLBW infants with PRF depends on the severity of illness rather than on the initial surgical approach.

Methods: Demographic, clinical, and outcome data on all VLBW infants were abstracted prospectively over a 12½-year period. Infants with PRF were stratified by PD or by LAP. Illness acuity was compared using the sum of a 7-point scoring system based on the clinical signs determined to be of prognostic significance. The factors associated with adverse outcome and the epidemiology of PRF were also examined.

Results: Of 937 infants, 78 with PRF required surgical intervention, consisting of PD in 32 (41%) and LAP in 46 (59%). Mean birth weight, illness acuity score, and the number of infants with NEC were significantly lower in PD ($P = .0005$). A higher proportion of PD infants received indomethacin ($P = .01$). There were no other differences between the 2 groups. Regardless of the choice of procedure, birth weight did not affect mortality rate; however, a shorter interval between PRF identification and surgical intervention was associated with improved survival rate ($P = .001$). Postoperative liver dysfunction, short gut syndrome, and enteric stricture were more common among LAP. Mortality rate, however, did not differ. When severe thrombocytopenia ($P < .03$) or neutropenia was present ($P < .03$), outcome of LAP was better than PD. Rescue LAP for 8 of rapidly deteriorating PD infants saved 5. Regardless of surgical approach, coagulopathy ($P < .003$), severe thrombocytopenia ($P < .005$), neutropenia ($P < .0001$), and multiple organ failure ($P < .0001$) were all predictive of fatality.

Conclusions: Choice of surgical approach should be based on the underlying illness and not on birth weight. In the presence of clinical indication of necrotic gut, or profound abdominal infection, LAP is a better choice. PD, however, is far less morbid and should be considered for isolated PRF. Rescue LAP must be considered without delay when PD fails.

INDEX WORDS: Bowel perforation, necrotizing enterocolitis, indomethacin, peritoneal drainage, laparotomy, nonionic contrast imaging.

TRADITIONAL SURGICAL management of neonatal bowel perforation (PRF) has been based on established surgical principles of laparotomy (LAP), resection of necrotic bowel, debridement, and exteriorization.[1] In the 1970s, however, bedside peritoneal drainage (PD) emerged as a palliative procedure for infants too ill to undergo LAP.[2] The facility with which PD can be accomplished has stimulated its increasing acceptance as appropriate definitive therapy and has resulted in numerous reports of equal or better outcome when compared with traditional LAP.[3-5] In many centers, PD has now become the routine approach, regardless of severity of the underlying illness.[6,7] Recent reports challenge the role of LAP as an initial choice of surgery and suggest that PRF, including those associated with underlying pathophysiologic process of necrotizing enterocolitis (NEC), require a far less invasive surgical approach for adequate initial management.[6-9]

We sought to investigate the relationship between outcome and surgical management of PRF in very low-birth-weight infants (VLBW). We hypothesized that severity of disease, rather than choice of surgical approach, dictated outcome for PRF. This report reviews 12½ years of clinical experience from a single regional perinatal center, examining initial surgical approach, clinical factors associated with adverse outcome, and the epidemiolgy of PRF.

MATERIALS AND METHODS

From January 1990 to June 2002, all infants with birth weight ≤1,200 g (VLBW) who were admitted to our neonatal intensive care

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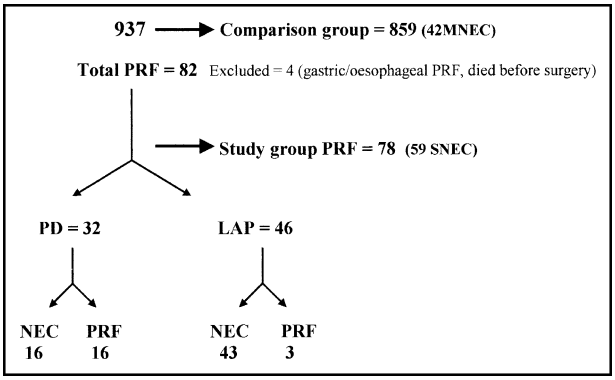

Fig 1. Diagram of the study plan. MNEC, medical NEC; SNEC, surgical NEC.

unit with PRF were entered into this prospective study. These infants constituted the study group. Infants with PRF were stratified as LAP or PD based on the initial surgical procedure. Those with gastric or esophageal perforations, with congenital gastrointestinal anomalies, chromosomal anomalies, or birth weights of ≤400 g were excluded. Evaluations performed at the onset of illness included abdominal radiograph, complete blood cell count, blood culture, arterial blood gas, and serum electrolytes. Tests were repeated as indicated clinically. Illness acuity was quantified by computing the sum of a 7-point scoring system with 1 point each for preoperative thrombocytopenia (platelet count $< 100{,}000/mm^3$), metabolic acidosis (calculated base deficit ≥ 10 mmol/L), neutropenia (absolute neutrophil count $< 2{,}000/mm^3$), left shift of segmented neutrophils (≥0.18), hyponatremia (serum sodium ≤ 130 mmol/L), bacteremia (culture confirmed), and hypotension (mean arterial blood pressure < adjusted gestational age). Thrombocytopenia was also subclassified into a severe category as indicated by platelet count $<50{,}000/mm^3$. Demographic, outcome, and surgical data were collected weekly or biweekly by chart review. A single pediatric radiologist evaluated all radiographs, and a pediatric pathologist examined tissue specimens. The presence of NEC in infants with PRF was confirmed by a combination of radiographic, pathologic, and postmortem findings of involved bowel by a pediatric pathologist. The study protocol was approved by the hospital Institutional Review Board.

Comparisons were made using 2-tailed student's *t* test, by χ^2, and by Fisher's Exact test. Univariate and multivariate logistic regression analyses were performed to determine the relationships between clinical findings and outcome. The impact of birth weight and of underlying illness on outcome based on the surgical option chosen was also investigated. Mantel-Haenszel methods were used to test for associations between LAP versus PD as well as mortality while controlling for neutropenia, bacterial infection, severely low platelet count, and NEC versus isolated perforations (PRF). The Breslow-Day test for homogeneity of odds ratios was also performed. Data are expressed as the mean ± SD, the odds ratio (OR) with 95% confidence intervals (CI), and as a relative risk (RR) ratio. Analyses were performed using SAS, version 8.2.[10] Values of $P \leq .05$ were considered significant.

RESULTS

A total of 1,003 VLBW infants were admitted to our neonatal intensive care unit (NICU) during the study period. Of these, 66 were excluded. Within the remaining population of 937 infants, 78 (8.3%) underwent an operative procedure for PRF (Fig 1). The initial choice of operative procedure was PD in 32 (41%) and LAP in 46 (59%). Nineteen (24%) of all PRF were isolated, whereas 59 (76%) were associated with NEC. Although mean birth weight of PD infants was lower than that of LAP infants (827 ± 226 *v*. 937 ± 203 g; $P < .03$, Table 1), there was no difference in gestational age at birth (25.9 ± 2.2 *v*. 26.9 ± 2.2; *P* value, not significant). The clinical acuity score was higher in LAP infants (4.5 ± 1.8 *v*. 3.0 ± 1.7; $P = .0005$) than in PD infants. A higher number of PD infants had received indomethacin (87% *v*. 61%; $P = .01$) before PRF as part of their ongoing medical management. A higher number of infants with NEC (93% *v*. 50%; $P < .0001$) received LAP than PD. With respect to outcome, liver dysfunction (54% *v*. 22%; $P < .005$), short gut syndrome (46% *v*. 9%; $P < .001$), and enteric stricture (43% *v*. 12%, $P < .005$) were more common among LAP infants. LAP infants required significantly longer hospitalization (111 ± 64 *v*. 75 ± 51; $P = .01$). Despite a higher number of infants with NEC and a higher illness acuity score in LAP infants, there were no differences in mortality rate between LAP and

Table 1. Characteristics and Outcome of Infants With Bowel Perforation

Characteristic	PD (n = 32)	LAP (n = 46)	*P* Value
Demographics and clinical characteristic			
Birth weight (g)	827 ± 226	937 ± 203	<.03
Gestational age at birth (wk)	25.9 ± 2.2	26.9 ± 2.2	NS
Females (%)	14 (44)	19 (41)	NS
African-Americans (%)	24 (75)	31 (67)	NS
Intraventricular hemorrhage (IVH) (%)	14 (43)	19 (56)	NS
Hyaline membrane disease (HMD) (%)	29 (91)	36 (78)	NS
Use of indomethacine (%)	28 (87)	28 (61)	.01
Age at onset (d)	11 ± 6	14 ± 8	NS
Interval between onset of illness and surgery (h)	57 ± 6	80 ± 8	NS
Clinical acuity score	3.0 ± 1.7	4.5 ± 1.8	.0005
Necrotizing enterocolitis (NEC) (%)	16 (50)	43 (93)	<.0001
Bacteremia (%)	23 (72)	35 (76)	NS
Peritonitis (%)	23 (72)	40 (87)	NS
Outcome			
Length of hospitalization (d)	75 ± 51	111 ± 64	.01
Total number of infections after PRF	1.7 ± 1.1	1.8 ± 1.2	NS
Liver dysfunction (%)	7 (22)	25 (54)	<.005
Short gut syndrome (%)	3 (9)	21 (46)	<.001
Enterocutaneous fistula (%)	7 (22)	6 (13)	NS
Stricture (%)	4 (12)	20 (43)	<.005
Mortality rate (%)	15 (47)	20 (43)	NS

NOTE. Results are expressed as mean ± SD. level of significance, $P \leq .05$; NS, $P > .05$.

Abbreviation: NS, not significant.

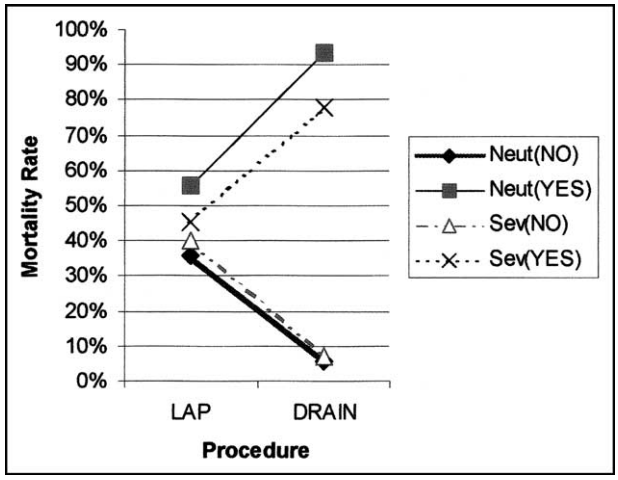

Fig 2. Association between surgical procedures and mortality in relationship to severe thrombocytopenia (Sev) and neutropenia (Neut).

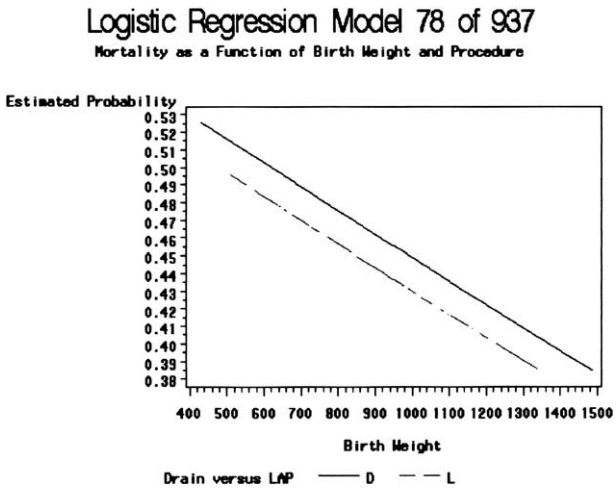

Fig 3. Relationship between birth weight and mortality rate of infants with bowel perforation.

PD infants (47% *v*. 43%; *P* value, not significant). Irrespective of surgical choice, the predictors for increased mortality rate were coagulopathy ($P < .003$), neutropenia, ($P < .0001$), severe thrombocytopenia ($P < .005$), and multiple organ failure ($P < .0001$). With respect to surgical choice, Mantel-Haenszel analyses (Fig 2) showed that when severe thrombocytopenia was present, mortality rate in LAP infants was lower than in PD infants (46% *v*. 78%; OR, 0.23; 95% CI, 0.06, 0.08; $P < .03$). Similarly, when neutropenia was present, mortality rate in LAP infants was lower than in PD infants (56% *v*. 93%; OR, 0.09; 95% CI, 0.01, 0.83; $P < .03$). However, mortality rate with LAP was higher than with PD when neither severe thrombocytopenia (40% *v*. 7%; OR, 8.7; 95% CI, 0.88, 85; $P < .05$) nor neutropenia was present (36% *v*. 6%; OR, 8.9; 95% CI, 1.02, 77.31; $P < .03$). Further, univariate logistic regression analyses for association between PD, clinical factors, and mortality rate showed that the odds of mortality with PD were higher when severe thrombocytopenia, bacteremia, neutropenia, persistent metabolic acidosis, and concurrent presence of NEC were present (Table 2). Five of 8 deteriorating infants with PD who underwent secondary "rescue" laparotomy survived. A shorter interval between onset of signs of illness and surgery also improved survival rate ($P < .0005$).

Table 2. Logistic Regression Model of Risk Factors and Outcomes for PD Infants Versus LAP Infants

Mortality = yes, Drain = yes	OR	*P* Value	CI
Necrotizing enterocolitis	1.35	.37	0.40-4.52
Coagulopathy	4.42	<.003	1.67-11.75
Neutropenia (absolute neutrophil count < 2,000/mm^3)	8.25	<.0001	2.95-23.07
Bacteremia	3.26	<.05	1.04-10.17
Severe thrombocytopenia (< 50,000/mm^3)	4.39	.005	1.55-12.39
Metabolic acidosis (Base deficit ≥ −10 mmol/L)	5.56	.001	1.99-15.53

NOTE. Level of significance, $P \leq .05$.

From an epidemiologic perspective, 12 (20%) of 59 infants with NEC in both the PD and LAP groups did not show characteristic radiographic signs including pneumatosis, portal venous gas, or pneumoperitoneum. Similarly, 9 of 19 infants with PRF did not have pneumoperitoneum despite PRF. Four of these 9 infants with PRF were identified through nonionic contrast gastrointestinal radiographs.[11] The remaining 5 presented with nonspecific signs including gasless or fixed bowel loops, fluid in the peritoneum, ascitis, or a discolored bluish abdomen. Within the population of 937 VLBW infants, the overall incidence of PRF was 8.3%. Almost 25% of perforations occurred as isolated events without the presence of NEC. When NEC was present, odds of PRF increased by approximately 60 times (OR, 60.50; 95% CI, 33.12, 110.40; $P < .0001$). In this situation, PRF then increased the mortality rate of these NEC infants by approximately 3.2 times (OR, 3.17; 95% CI, 2.01, 5.10; $P < .0001$). The effect of PRF is also apparent in the fact that the odds of mortality in infants who underwent PD for whatever reason were 3.2 times higher than in infants without PRF (OR, 3.20; 95% CI, 1.60, 6.50; $P < .003$). Logistic regression analyses did not show any significant differences between PD and LAP procedure with respect to birth weight (Fig 3). The distribution of infants with NEC-associated PRF did not change significantly before and after 1995. Conversely, 79% of all PRF not associated with NEC occurred after 1995 ($P < .01$), when routine indomethacin prophylaxis against intraventricular hemorrhage in VLBW infants was initiated in our center.

DISCUSSION

The 12½ years of this study have witnessed numerous advances in care of the VLBW infant. Among them have been an overall improvement in survival rate of all tiny premature infants[12] use of indomethacin prophylaxis for intaventricular hemorrhage,[13] and the emergence of PD as a less-invasive, and purportedly equally effective method of management of PRF.[6-9] Our initial intent was to determine whether there really was any significant difference in outcome between infants undergoing PD versus those whose treatment followed the more established "tradition" of surgical exploration.[1] As indicated by the clinical acuity score, despite the fact that LAP babies were actually more ill, the overall mortality rate between PD and LAP was no different. The higher morbidity rate associated with LAP can be attributed to the fact that the majority of infants with NEC associated PRF were managed with surgical exploration of a disease that is characterized by polymicrobial infection associated with destruction and disruption of the gastrointestinal tract.[14] Effective PD will theoretically evacuate peritoneal gas, pus, and stool, thereby minimizing operative stress and avoiding intestinal resection.[2] This presents PD as an attractive alternative to laparotomy. Failure to remove necrotic bowel, however, will propagate continued septic insult to the patient and prolong the partially treated illness for a much longer time, often culminating in death.[15,16] Thus, the decision to explore must be based on assessment of patient stability and the likelihood of existence of necrotic tissue that requires immediate excision.[16,17] As illustrated in Fig 2 and in Table 2, in the presence of symptoms suggestive of an underlying severe inflammatory or necrotic process, LAP continues to have a definite role as a surgical procedure in VLBW infants[8,18] especially when birth weight alone has no significant impact on mortality with respect to choice of procedure (Fig 3).[8,1] Analysis of factors contributing to outcome clearly identified a subgroup of infants who do not manifest an ongoing extensive necrotic or inflammatory process with PRF for whom PD is most suitable.[8,9] It is also apparent from this investigation that the advantage of PD is offset by delay in diagnosis of PRF. The primacy of expediency is further reinforced by analysis of the entire group where time to surgical intervention after PRF diagnosis was significantly shorter in survivors. Again, to emphasize the critical importance of timing, the presence of either of the 2 indicators of severe disease (neutropenia or severe thromboycytopenia) eliminated this difference and was associated with equally poor survival rate, indicating that the mortality rate is determined by severity of underlying disease rather than the choice of procedure.[15,16] If it is not the procedure, then it must also be the timing of the procedure. Delay until sepsis has become so advanced as to undermine coagulation and organ function will yield poor results, regardless of surgical approach.[15-20]

Advanced disease, as reflected by severe thrombocytopenia and neutropenia, is a significant predictor of fatality. Despite its apparent usefulness, PD clearly is a less-successful approach for these infants. Isolated PRF with no evidence of advanced disease, on the other hand, is associated with a significantly better outcome from PD (Fig 2). What is less well defined, however, is the proportion of infants with isolated PRF for whom PD may have avoided the complications of LAP. Clearly, LAP in the face of isolated PRF is excessively morbid.

This last question, especially as viewed from the perspective of avoidable cost, is relevant to centers that continue to provide regional perinatal services. These hospitals are often "safety-net" institutions in which high-cost, low reimbursement problems like NEC tend to aggregate.[12,20,22] It is critical, therefore, that perinatal centers remain committed to controlling the personal, physical, emotional, social, and societal devastation of NEC. Whereas the best method is effective prevention, reality mandates that a management protocol based on clinical evidence and measured effect be constantly followed and monitored.

Such a management protocol clearly must include immediate drainage of any infant who presents with sudden intraperitoneal free air.[9,18,19] In the absence of symptoms of enteric or systemic inflammation, expeditious drainage of the pneumoperitoneum will avoid unnecessary spread of contamination, and, based on evidence in this and other reports, will usually be followed by a relatively uncomplicated, successful clinical course.[9,15-20] Of equal importance to the "benign" postoperative course followed by infants with PD for isolated PRF is the apparent "rescue" of 5 of 8 babies for whom initial PD produced no immediate clinical improvement. These babies obviously required more aggressive excision of infected tissue and manifest this need by continuing to deteriorate despite PD placement.

Considering the increasing incidence of isolated PRF[8,11,13] and the effect of expeditious rescue laparotomy in the face of failed PD, modern surgical management of PRF in the VLBW infant must continue to amalgamate the clinical skills of the neonatologist and the neonatal surgeon. Such protocols must include immediate PD for all infants with isolated PRF, careful assessment of the presence or progression of signs of NEC, and timely operative intervention for those babies in whom extensive irrigation and debridement is determined to be mandatory. Like so many things in modern medicine, one size does not fit all. Multiple sizes, however, especially when applied to infants of the most dimunitive size, will clearly lead to better outcome,

healthier infants, and a more satisfying quality of life for all.

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