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Peritoneal drainage does not stabilize extremely low birth weight infants with perforated bowel: data from the NET Trial☆

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Abstract

Introduction: Proponents of peritoneal drainage (PD) hypothesize that it allows stabilization before laparotomy. We examined this hypothesis by comparing clinical status before and after either PD or primary laparotomy (LAP).

Methods: In an ethically approved, international, prospective randomized controlled trial (2002-2006), extremely low birth weight (<1000 g) infants with pneumoperitoneum received primary PD (n = 35) or LAP (n = 34). Physiologic data were collected prospectively and organ failure scores calculated and compared between preprocedure and day 1 after procedure. Data, expressed as mean ± SD or median (range), were analyzed using appropriate statistical tests.

Results: There was no postprocedure improvement in either PD or LAP group comparing heart rate (PD, $P = 1.0$; LAP, $P = .6$), blood pressure (PD, $P = .6$; LAP, $P = .8$), inotrope requirement (PD, $P = .2$; LAP, $P = .3$), or Arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PD, $P = .1$; LAP, $P = .5$). Infants managed with PD had a worsening cardiovascular status ($P = .05$). There were no differences in total organ failure score in either group (PD, $P = .5$; LAP, $P = 1$). Only 4 infants survived with PD alone with no difference between preprocedure and postprocedure organ failure score ($P = .4$).

Conclusions: Peritoneal drainage does not immediately improve clinical status in extremely low birth weight infants with bowel perforation. The use of PD as a stabilizing or temporizing measure is not supported by these results.

Peritoneal drainage (PD) was first proposed as a treatment of bowel perforation in extremely low birth weight infants in 1974 by Ein et al [1]. It has become a widely used treatment, with some surgeons using it as a temporizing measure [2-4] and others as definitive treatment [5-8]. We have reported that 95% of UK pediatric surgeons use PD as an option in the

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management of infants with necrotizing enterocolitis (NEC) [9]. There have been 2 randomized controlled trials comparing PD with primary laparotomy in this group of extremely unstable neonates. Neither trial showed a survival advantage with the use of peritoneal drainage, and secondary outcomes including length of stay were similar in both groups [10,11]. Some have interpreted these findings as a reason to support the increased use of PD as a less invasive measure [12].

The aim of this study was to investigate the hypothesis that primary PD allows stabilization of an extremely sick neonate, so that a subsequent laparotomy may be carried out more safely. The hypothesis was tested by comparing physiologic variables and organ failure scores before and after PD or primary laparotomy in the context of a randomized controlled trial.

1. Methods

1.1. Trial methodology

The NET trial was a multicenter, international, randomized controlled trial undertaken in 31 neonatal intensive care units in 13 countries from 2002 to 2006. The method has been described in detail elsewhere [10].

Infants weighing 1000 g or less with bowel perforation demonstrated as pneumoperitoneum on abdominal radiograph were included. Patients were excluded if they had had previous episodes of NEC, a previous laparotomy or peritoneal drain, bilateral grade 4 intraventricular hemorrhage [13], or were treated in a neonatal intensive care unit where access to pediatric surgeons was not available. Each center had ethical approval (MREC/02/2/34 in the United Kingdom), and the trial was registered (ISRCTN18282954).

Infants were randomized by weighted minimization [14] to primary laparotomy (n = 34) or primary peritoneal drain (n = 35). The protocol specified that at least 12 hours should be allowed after drain insertion before performing a delayed laparotomy, if clinical deterioration occurred.

1.2. Data collection

Data on physiologic variables including heart rate, mean arterial pressure, inotrope requirement, type and details of ventilation, and arterial partial pressure of oxygen / fraction of inspired oxygen (PaO_2/FiO_2) ratio were collected prospectively before randomization and on day 1 after treatment. Ventilation requirement was graded as 0 if the infant was breathing spontaneously, 1 if requiring continuous positive airway pressure ventilation by face mask alone, 2 if mechanically ventilated, and 3 if requiring high frequency oscillatory ventilation.

Organ failure scores for cardiovascular, respiratory, hepatic, renal, and coagulation status were calculated using a modified sequential organ failure assessment score [15] (Table 1) and compared between preprocedure (PD or primary laparotomy) and day 1 after procedure. A percentage score was calculated for each patient based on available data and multiplied by 20 to allow comparison on a scale of 0 to 20.

2. Statistical methods

Data are expressed as mean ± SD if normally distributed or median (range) if not and were analyzed using paired *t* test, Wilcoxon's test, and Fisher's Exact test as appropriate using GraphPad Prism (v4.03), GraphPad Instat (v3.06) (GraphPad Software Inc, San Diego, Calif), and SPSS (v15.0; SPSS Inc, Chicago, Ill). $P \leq .05$ was regarded as significant.

3. Results

There were no demographic differences between infants in the PD group and the LAP group, including no difference

Table 1 Modified sequential organ failure assessment score [15]

Organ system	Variable	Score				
		0	1	2	3	4
Respiratory	PaO_2/FiO_2 (mm Hg)	>400	≤400	≤300	≤200	≤100
Renal	Urine output (mL/kg per hour)	≥1		<1	<0.5	Anuria
Hepatic	Total bilirubin (μmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular	Hypotension (doses in μg/kg per minute)	Normal BP	MAP< GA+ age (wk)	Dop ≤ 5 or Dobut (any dose)	Dop> 5 or Epi ≤ 0.1 or Norepi ≤ 0.1	Dop > 15 or Epi > 0.1 or Norepi > 0.1
Coagulation	Platelet count ($\times 10^3/mm^3$)	≥150	<150	<100	<50	<20 or transfusion

BP indicates blood pressure; MAP, mean arterial pressure; GA, gestational age; Dop, dopamine; Dobut, dobutamine; Epi, epinephrine; Norepi, norepinephrine.

Table 2 Changes in physiologic parameters for PD group and LAP group

Variable	PD			LAP		
	Pre	Post	*P*	Pre	Post	*P*
Heart rate (bpm)	153 ± 18	152 ± 24	1.0	159 ± 21	160 ± 16	.6
MAP (mm Hg)	41 ± 11	40 ± 9	.6	39 ± 10	40 ± 8	.8
Inotropes (yes)	38%	55%	.2	41%	55%	.3
Pao_2/Fio_2 ratio	186 ± 99	231 ± 115	.1	183 ± 116	197 ± 116	.5

Pre indicates preprocedure; Post, postprocedure; bpm, beats per minute.

in age (9.5 days in LAP group [range, 3-32] vs 9 days in PD group [0-39]; *P* = .5), birth weight (749 ± 25 g LAP vs 719 ± 21 g PD; *P* = .4), or gestational age (26.4 weeks LAP vs 26.2 weeks PD; *P* = .7) [10].

Two infants were excluded from further analysis as delayed laparotomy was performed on the same day as PD insertion. Overall, delayed laparotomy was performed in 26 (74%) of 35 patients in the PD group, after a median of 2.5 days (range, 0.4-21).

3.1. Cardiovascular status

The were no significant differences between preprocedure and postprocedure heart rate or mean arterial pressure in the PD group or the LAP group (Table 2). Of 32 infants, 12 (38%) required inotropes preprocedure in the PD group, compared to 18 (55%) of 33 postprocedure (*P* = .2). In the LAP group, 13 (41%) of 32 required inotropes preoperatively and 16 (55%) of 29 postoperatively (*P* = .3). Infants managed with PD had a higher inotrope requirement (ie, higher score on the cardiovascular component of the organ failure score) (Table 3; *P* = .05), although their postprocedure inotrope requirement was similar to that of the LAP group as the LAP group had a lower preprocedure score than the PD group.

3.2. Respiratory status

The level of ventilatory requirement was not different in the PD group (preprocedure 2 [0-3] vs postprocedure 2 [0-3]; *P* = .3) or the LAP group (preprocedure 2 [0-3] vs postprocedure 2 [1-3]; *P* = .5). There was also no significant difference in the Pao_2/Fio_2 ratio (paired *t* test *P* = .1 in PD group; *P* = .5 in LAP group) (Table 2; Fig. 1). This resulted in no significant alterations in the respiratory component of the organ failure score (Table 3).

3.3. Renal, hepatic, and coagulation status

There were no significant alterations in renal, hepatic, or coagulation status preprocedure vs postprocedure in either the LAP or PD groups, as evidenced from the respective components of the organ failure score (Table 3).

3.4. Organ failure scores

There were no differences in composite organ failure score comparing preprocedure with postprocedure in either group (Table 3). Only 4 infants survived with PD alone; in these infants, there was no difference between preprocedure and postprocedure organ failure score (mean score preprocedure, 6.7 ± 2.1; postprocedure, 7.8 ± 2.2; *P* = .4).

4. Discussion

We have previously shown that peritoneal drainage does not improve survival in ELBW infants with bowel perforation and that most infants treated with PD required

Table 3 Organ failure scores (sequential organ failure assessment) for PD and LAP group (best = 0, worst = 4, median [range]), *P* values given for Wilcoxon's matched pairs tests

Organ system	PD				LAP			
	n	Pre	Post	*P*	n	Pre	Post	*P*
Respiratory	26	3 (1-4)	2 (0-4)	.3	16	3 (0-4)	3 (1-4)	.7
Renal	33	0 (0-3)	0 (0-3)	.3	25	0 (0-4)	0 (0-3)	.2
Hepatic	16	2 (0-3)	2 (0-4)	.9	16	2 (0-3)	2 (0-3)	.8
Cardiovascular	31	0 (0-3)	2 (0-4)	.052	29	2 (0-3)	2 (0-3)	.4
Coagulation	30	2 (0-4)	1.5 (0-4)	.9	25	1 (0-4)	1 (0-4)	.9
Total score (0-20)	33	7.4 ± 2.9	7.6 ± 2.8	.5 *	32	7.5 ± 4.3	7.6 ± 4.4	1.0 *

Pre indicates preprocedure; Post, postprocedure.

* *P* value for paired *t* test.

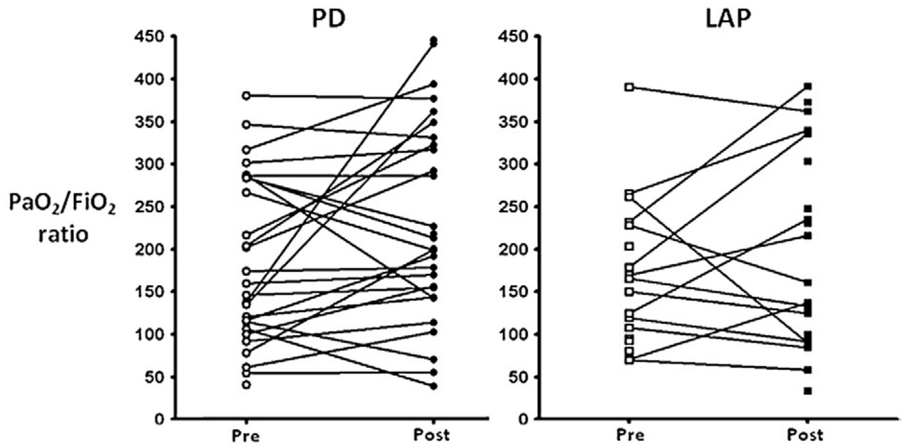

Fig. 1 Arterial partial pressure of oxygen (PaO_2) / Fraction of inspired oxygen (FiO_2) ratio in PD and LAP group comparing preprocedure (Pre) with postprocedure (Post) (P = .1 for PD; P = .5 for LAP).

a delayed laparotomy [10]. A randomized controlled trial performed concurrently with this study in the United States (NECSTEPS), which did not allow early laparotomy after PD, has also shown no difference in survival at 90 days between infants managed with PD and laparotomy [11]. The NECSTEPS trial randomized infants less than 1500 g with proven or suspected perforation to PD or primary laparotomy but discouraged the use of early "rescue" laparotomy. Of 55 of their patients, 5 (9%) required delayed laparotomy for clinical deterioration, compared to 26 (74%) of 35 in this trial. However, 16 further patients receiving PD in the NECSTEPS trial had a late delayed laparotomy for intestinal complications such as stricture. The NECSTEPS trial can therefore be seen as a trial of peritoneal drain as a definitive treatment, whereas the NET trial also allowed the concept of PD as a temporizing or stabilizing measure to be investigated. Despite this important difference in method, both trials found that survival was not improved by the insertion of a drain either as a definitive procedure or a temporizing measure.

A survey of pediatric surgeons in the United Kingdom we performed in 2002 confirmed that PD was a widely used technique for the management of neonates with bowel perforation. We found that 58% use PD as a definitive treatment, 57% to stabilize neonates before transfer, and 95% to stabilize before laparotomy [9].

Proponents of peritoneal drainage have argued that it allows stabilization of extremely unstable infants to allow laparotomy, but this analysis of patients in a randomized controlled trial does not support this hypothesis. There was no short-term improvement in any physiologic variable in infants managed with PD, compared to those managed with primary laparotomy. In infants managed with PD, there was a trend toward worsening cardiovascular status, with a worse postprocedure cardiovascular failure score.

A retrospective study comparing neonatal physiology (Score for Neonatal Acute Physiology Perinatal Extension, SNAPPE-II) scores in very low birth weight infants (<1500 g) with bowel perforation found that infants allocated to PD had higher than predicted mortality based on the SNAPPE-II score, even after correcting for their worse initial scores [16]. The mortality in infants managed with primary laparotomy was in keeping with the predicted rate from the SNAPPE-II score. Other authors have attempted to assess whether this score could be used to guide therapy in this group of infants and found that there was no difference in scores between very low birth weight infants managed with PD alone and PD followed by laparotomy on the day after drain insertion but that modified SNAPPE scores (with correction for birth weight excluded) fell after initial drainage, indicating physiologic improvement [17]. It was not possible to calculate these scores for our patients as data on seizures and Apgar scores were not collected in the trial.

This study represents a post hoc analysis of a randomized controlled trial that was powered to detect changes in mortality not in individual short-term physiologic variables. Also, we are only able to compare preprocedure results with results on day 1 after the procedure, as data were not collected immediately after the procedure or at a specified time-point (eg, 12 hours) after the initial procedure. It is extremely unlikely that improvement in physiologic parameters occurred after 24 hours from PD insertion. Nevertheless, the data are important because they represent the results of a prospective trial with patients allocated to treatment by weighted minimization (a form of randomization), in contrast to all other retrospective studies where infants managed with peritoneal drainage were sicker than those allocated to primary laparotomy [18]. If there were an immediate improvement in physiologic status after peritoneal drainage, this would be expected to be reflected in a sustained improvement in clinical status, at least until the next day, if the improvement is to be considered clinically important, which would have been detected by this study design. Of note, 2 patients randomized to PD insertion received a laparotomy during the first 24 hours because of clinical deterioration. Data from these patients were not included in analysis, further supporting the concept that PD insertion does not improve the clinical status of patients.

Our results therefore do not support the widely held view that PD is a safe alternative to laparotomy in ELBW infants with bowel perforation nor that it is an effective temporizing measure. We therefore advocate the use of early laparotomy in infants with bowel perforation.

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Discussion

Mark Davenport (London, United Kingdom): "Can you remind everyone of what the outcome of the NET trial was? What you have shown is that there is no difference physiologically after day one in all the indices you have looked at between peritoneal drainage and laparotomy. Could you remind us, because I don't think you showed it here, what actually happened to these babies?"

Clare Rees (response): "There was no difference in mortality, being about 45% in both groups, but if anything there was a trend to a better outcome in the laparotomy group. Furthermore, 74% of infants who had a peritoneal drain then required a laparotomy after their drain. Only 4 survived who had had a drain alone. Of those infants who had laparotomy after a drain, they did a little better but not significantly different to the ones who were managed by drain alone."

Jeffrey Brain (Cambridge, United Kingdom): "May I say that this study rather misses the point. By randomizing the patients, you don't treat them in any specific way. I suggest that drainage is very useful in those patients with perforation where there is such gross splinting of the diaphragm that you cannot ventilate them—if you drain them and then do the laparotomy as soon as you can, that is advantageous. This study does not take this into account."

Clare Rees (response): "Many surgeons have used the drain and then found the baby easier to ventilate afterwards. Trial patients were randomized as soon as the diagnosis of pneumoperitoneum was made so there wasn't a delay in regard to primary treatment. Thus, in the published paper, we showed that all the physiological variables were equal between the 2 groups. Now if you look at this slide you will see that some patients did really well in terms of ventilation after their drain, and these are the ones that we might remember, in other patients there was no difference and in other patients they deteriorated. The same is true for the laparotomy group. I don't believe (as a result of this randomized trial) that peritoneal drainage does anything while you are waiting to do a laparotomy, and I believe that we should go ahead and do a laparotomy as soon as possible."

Jeffrey Brain (Cambridge, United Kingdom): "I quite agree with that, but very often, a situation occurs before transfer, and there may be 2 or 3 hours during which transfer is taking place, so a drain before transfer saves these babies as it allows ventilation and then when they get to the center. That is the time when you randomize them, and they need a laparotomy not the drain, which should have been done before."

Clare Rees (response): "Of course this trial was done in centers with pediatric surgeons, and I can't really comment on the management of neonates in nonsurgical centers because there is nothing we can do to influence their management because we are not there."

Jeffrey Brain (Cambridge, United Kingdom): "You can, you can put a drain in, or at least, the transport team can!"

Keith Georgeson (response): "In the USA, our comparable NEC study showed no difference between the 2 groups. But, it is interesting that all our surgeons following this study now prefer exploration to drainage. The one group though that we thought benefited by drainage is the isolated group—those with a dime size perforation. Many of them never come to surgery, and they do very well if you drain them; can you comment on that disparity from your analysis?"

Clare Rees: "Last year at EUPSA, we presented on how good a surgeon is at detecting whether a baby had an isolated perforation or perforated NEC and whether a drain was more beneficial in a group who were subsequently found at laparotomy to have a isolated perforation. Since most of our patients received a laparotomy, we were able to make that diagnosis. We found that surgeons were not particularly good at the diagnosis preoperatively, and there was no difference in outcome with those who had a drain compared to those who had a laparotomy.