Outcome in definite and advanced neonatal necrotizing enterocolitis

Anita Roy, *MS, FRCS,* ***Maen Tayeb,*** *FACHARZT,* ***Suzie Al-Khogeer,*** *ABGS.*

ABSTRACT

Objective: To evaluate and compare the outcome of newborns with definite (Bells stage II) and advanced (Bells stage III) necrotizing enterocolitis (NEC) and to assess the role of primary peritoneal drainage.

Methods: This study was conducted in the Department of Pediatric Surgery, Maternity and Children's Hospital, Dammam, Kingdom of Saudi Arabia. Medical records of all cases diagnosed with NEC or suspected NEC between May 1993 and June 2003 were reviewed retrospectively. A total of 67 cases meeting the criteria for Modified Bells stage II and III disease were selected for the study. Twenty-five (37%) cases were treated medically and 42 (63%) needed surgical intervention, namely primary peritoneal drainage (PPD) with or without salvage laparotomy (SL) (n=25), or primary laparotomy (PL) (n=17). Data regarding patient demographics, neonatal history, clinical presentation, laboratory and radiological features, operative findings, complications and mortality were collected and compared between the medical and surgical group and between the 2 surgical groups.

Results: The overall mortality was 37%, 8% in the medical group versus 55% in the surgically treated group. The PPD group had the highest mortality (72%) versus 29% in the PL group. In the PPD group, 14 (56%) needed SL and only 3 (12%) survived without laparotomy. The mean gestational age and birthweight were 32.1 weeks and 1713 gms in the PPD group as compared to 35.7 weeks and 2484 gms in the PL group. The PPD group were more critically sick than the PL group. The average length of time from onset to laparotomy was longer, 6.6 days in the PPD group versus 2.2 days in the PL group. In the 31 cases undergoing laparotomy, the terminal ileum was involved most frequently followed by the cecum and right colon. The PPD + SL group had a higher mortality in isolated, multifocal, and pan involvement of bowel when compared to the PL group. All babies with only isolated involvement in the PL group survived.

Conclusion: The surgical mortality of NEC in our hospital is very high due to advanced disease. The PPD group in our study fared badly, as it comprised a poor risk group with ongoing sepsis, with the bias being in favor of PPD as these babies were unfit to undergo major surgery. Early SL after PPD in those showing signs of persistent disease may improve the outcome in this group.

Saudi Med J 2004; Vol. 25 (6): 746-752

As a result of increased survival of premature and extremely low birthweight babies secondary to technical advancements, neonatal necrotizing enterocolitis (NEC) has emerged as the most common gastrointestinal emergency in the neonatal intensive care unit (NICU).[1] The mortality rate of surgically treated babies with NEC, however, remains high and can vary depending on gestational age, birth weight, comorbid conditions and extent of disease. Approximately 90% of neonates developing NEC are premature[1] and the classical surgical management of perforated NEC is laparotomy with resection of affected bowel.[2] However, many of these babies with low birth weight and associated

From the Department of Pediatric Surgery, Maternity and Children's Hospital, Dammam, *Kingdom of Saudi Arabia*.

Received 8th October 2003. Accepted for publication in final form 9th February 2004.

Address correspondence and reprint request to: Dr. Anita Roy, Consultant Pediatric Surgeon, Department of Pediatric Surgery, Maternity and Children's Hospital, PO Box 2595, Dammam 31176, *Kingdom of Saudi Arabia*. Tel. +966 (3) 8426666. Fax. +966 (3) 8422828. E-mail: anitaroysa@hotmail.com

comorbid conditions are unfit for major surgery. Since Ein et al[3] described peritoneal drainage as a temporizing procedure in 1977,[3] it has become popular as the initial surgical intervention particularly in high-risk severely compromised babies. Several reports have even advocated PPD as a definitive procedure.[4-7] Debate however, continues whether PPD or primary laparotomy (PL) is superior. At our institution, PPD is used for premature, small or critically sick babies and PL for babies fit for major surgery under general anesthesia. Over the years, we noticed a much higher rate of mortality in the PPD group even after salvage laparotomy (SL), and since NEC continues to be one of the most frequent conditions requiring surgical intervention, we designed this retrospective study to evaluate the outcome of neonates with confirmed NEC treated in our hospital over the last 10 years and to study the reasons for the poor outcome in those treated with PPD with or without SL as compared to those treated medically or with primary laparotomy.

Methods. A retrospective review of the medical records of all neonates with a diagnosis of NEC or suspected NEC treated at Maternity and Children's Hospital, Dammam, Kingdom of Saudi Arabia over a period of 10 years from May 1993 to June 2003 was carried out. Only 67 cases met the criteria of Modified Bells Stage II and III NEC.[8] Data collected included gestational age, birth weight, gender, Apgar scores at one and 5 minutes, respiratory or circulatory collapse at birth requiring support, associated cardiac or non-cardiac comorbid conditions, umbilical vessel (umbilical artery or umbilical vein) cannulation, feeding history, clinical signs and symptoms, age at onset and at laparotomy, laboratory and radiological parameters, management modalities, operative findings, histopathological reports, complications, and outcome (death or discharge from the hospital). The medical management consisted of broad spectrum antibiotics, withholding of feeds, gastrointestinal decompression with a nasogastric tube, intravenous fluids, observation for progress of abdominal signs, monitoring blood gases, complete blood count, blood urea and electrolytes, and instituting ventilatory or circulatory support as required. Serial abdominal radiographs in the supine and lateral decubitus positions were obtained in all cases. Definite indications for surgical intervention included pneumoperitoneum, persistent abdominal wall erythema, abdominal mass or fixed bowel loops on serial abdominal radiographs, with signs of persistent sepsis or clinical deterioration. In very low birth weight babies or full term critically sick babies, PPD at the bedside was the initial surgical intervention. In good weight, low risk babies with pneumoperitoneum or progressive abdominal signs, in spite of adequate medical treatment, a primary laparotomy (PL) was undertaken. A SL in the PPD group was carried out in those with progressive disease and relatively fit to undergo major surgery. Some of our babies however, died before this could be carried out. The medically treated group was compared with the surgical group and in the surgical group the PPD group was compared with the PL group, with regard to patient demographics and neonatal history, (**Table 1**), clinical and laboratory features (**Table 2**) and, radiological parameters. Significant thrombocytopenia was arbitrarily defined as at least 3 consecutive platelet counts <100,000/cu. mm, and significant neutropenia as consecutive white blood cell counts <4000/cu mm. In 31 neonates who underwent laparotomy, the extent of bowel involvement was correlated with mortality in the SL and PL groups (**Table 3**). The extent of bowel involvement is classified according to the criteria adopted by Fasoli et al[9] as, "Isolated" NEC, defined as a single or a short segment of intestine with gross evidence of full thickness necrosis or perforation. "Multifocal" NEC, defined as 2 or multiple segments of intestine involved in NEC, which appears to be full thickness necrosis and "Panintestinal" is the involvement of majority of small and large bowel. A final comparison between the SL group and the PL group in terms of mean birth weight and gestational age, mean age at onset of NEC, mean number of days from onset to laparotomy, associated cardiac and non-cardiac comorbid conditions and mortality is shown in **Table 4** for further comprehension of the differences between these groups.

Results. A total of 67 neonates made up the study group, 42 (63%) of them underwent surgical intervention and 25 (37%) were treated medically. Only 2 babies (8%) died in the medically treated group. Amongst the surgically treated group, 25 had PPD, and 17 had PL. The total surgical mortality was 55%. In the PPD group 14 (56%) did not improve and had SL and 8 (32%) died without laparotomy. In the PL group, only 5 (29%) died when compared to 72% in the PPD group. On comparing the demographics and neonatal history between the medical and surgical group (**Table 1**), mean birth weight and gestational age are more or less similar with slightly lower apgar scores at one and 5 minutes in the surgically treated group, which had a 21% rate of circulatory collapse at birth when compared to only 4% in the medically treated group. The medically treated group had a higher rate of associated non-cardiac comorbid conditions (72%) versus 52% in the surgically treated group. Umbilical vessel cannulation and feeding history did not show much variation between these 2 groups. On comparing the same variables (**Table 1**), between the PPD and PL groups, the mean

gestational age was 32.1 weeks (24-40 weeks) in the PPD group versus 35.7 weeks (28-40 weeks) in the PL group and the mean birth weight was 1713 (800-3850 gms) in PPD group versus 2484gms, (800-4100 gms) in the PL group. Apgar scores were marginally lower in the PPD group, which had a higher incidence of respiratory and circulatory collapse at birth namely 48% and 28% versus 24% and 12%, in the PL group. The PPD group had a much higher rate of associated non-cardiac comorbid conditions (68%), than the PL group (29%). The PPD group had 56% incidence of umbilical vessel cannulation when compared to only 12% in the PL group. In the PPD group, 20% were unfed when compared to only 6% in the PL group. Comparison of the clinical features (**Table 2**), showed that the surgically treated group had more advanced disease with 88% meeting parameters for Bell stage III, while 100% of the medically treated babies were classified as Bell stage II. The surgically treated babies had much higher incidence of signs of peritonitis namely abdominal wall erythema was 71% and abdominal mass 21% versus 12% and 0% in the medically treated group. The surgically treated babies were also more critically ill with 71% and 67% incidence of respiratory and circulatory collapse when compared to only 28% and 8% in the medically treated group. The surgically treated group also had a much higher frequency of significant thrombocytopenia and persistent metabolic acidosis, 71% and 67% versus 36% and 16% in the medically treated group. *Candida sepsis* was 21% in the surgically treated group versus 8% in the medically treated group. Sixty percent babies in the surgically treated group had a positive blood cultures for gram negative bacteria when compared to 44% in the medical group. The same variables (**Table 2**) were compared across the 2 surgical groups and a noticeably higher

Table 1 - Patient demographics and neonatal history in the study groups.

Patient demographics	**Medical group (N=25)**	**Surgical group (N=42)**	**PPD group (N=25)**	**PL group (N=17)**
Gestational age (weeks)				
Range	27 - 40	24 - 40	24 - 40	28 - 40
Mean	33.4	33.6	32.1	35.7
Birth weight (gms)				
Range	700 - 3700	800 - 4100	800-3850	800-4100
Mean	1951	1942	1713	2484
Apgar score at 1 minute				
Range	1 - 9	1 - 10	1 - 9	1 - 10
Mean	6.3	5.9	5.4	8.2
Apgar score at 5 minutes				
Range	5 - 10	1 - 10	5 - 10	1 - 10
Mean	8.5	7.9	7.5	8.2
Resp. collapse at birth (%)	11 (44)	17 (40)	12 (48)	4 (24)
Circulatory collapse at birth (%)	1 (4)	9 (21)	7 (28)	2 (12)
Associated significant cardiac comorbid anomalies at birth (%)	10 (40)	17 (40)	11 (44)	6 (35)
Associated significant non cardiac comorbid conditions (%)	18 (72)	22 (52)	17 (68)	5 (29)
Umbilical vessel cannulation (%)	10 (40)	16 (38)	14 (56)	2 (12)
Feeding history				
Fed (%)	22 (88)	36 (86)	20 (80)	16 (94)
Not fed (%)	3 (12)	6 (14)	5 (20)	1 (6)
Gender				
Males (%)	11 (44)	22 (52)	12 (48)	10 (59)
Females (%)	14 (56)	20 (48)	13 (52)	7 (41)
Male to female ratio	1 : 1.3	1 : 0.9	1:1.1	1:0.6

PPD - primary peritoneal drainage, PL - primary laparotomy, Resp. - respiratory

Table 2 - Clinical features in the study groups.

Clinical features	Medical group (N=25)	Surgical group (N=42)	PPD group (N=25)	PL group (N=17)
Age at onset (days)				
Range	2 - 50	2 - 45	2 - 45	3 - 31
Mean	10.2	10.8	14.1	6.2
Lethargy (%)	24 (96)	25 (60)	16 (64)	8 (47)
Vomiting or NGT aspirates (%)	23 (92)	36 (86)	20 (80)	16 (94)
Abdominal distension (%)	23 (92)	42 (100)	25 (100)	17 (100)
Abdominal wall erythema (%)	3 (12)	30 (71)	18 (72)	12 (71)
Abdominal mass (%)	NIL -	9 (21)	7 (28)	2 (12)
Bloody stools (%)	11 (44)	16 (38)	9 (36)	7 (41)
Respiratory collapse (during acute episode) (%)	7 (28)	30 (71)	21 (84)	9 (53)
Circulatory collapse (during acute episode) (%)	2 (8)	28 (67)	18 (72)	10 (59)
Bells' stage (%)				
II	25 (100)	5 (12)	5 (20)	1 (6)
III	-	37 (88)	20 (80)	16 (94)
Significant metabolic acidosis (%)	4 (16)	28 (67)	17 (68)	11 (65)
Significant thrombocytopenia (%)	9 (36)	30 (71)	21 (84)	9 (53)
Significance neutropenia (%)	9 (36)	20 (40)	14 (58)	5 (29)
Sepsis				
Positive blood culture (%)	11 (44)	25 (60)	15 (60)	10 (59)
Positive *Candida sepsis* (%)	2 (8)	9 (21)	7 (28)	2 (12)

PPD - primary peritoneal drainage, PL - primary laparotomy, NGT - nasogastric

Table 3 - Extent of disease and outcome in 31 operated cases.

Extent of disease	**PL (N=17)**		**PPD + SL (N=14)**		**Mortality**			
					PL group		**PPD + SL group**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Isolated NEC (full-thickness necrosis of one area only)	3	(18)	5	(36)	0/3	-	2/5	(40)
Multifocal NEC (2 or more segments of intestine with full thickness necrosis)	11	(65)	7	(50)	3/11	(27)	6/7	(86)
Pan - intestinal (majority of small and large bowel involved)	3	(18)	2	(14)	2/3	(67)	2/2	(100)

PPD - primary peritoneal drainage, PL - primary laparotomy, NEC - necrotizing enterocolitis

Table 4 - Primary peritoneal drainage and salvage laparotomy versus primary laparotomy.

Parameters	PPD + SL N=14	PL N= 17
Mean birth weight (gms)	1788 gm (850 - 3850)	2484 (800 - 4100)
Mean gestational age (weeks)	32.2 (24 - 40 weeks)	35.7 (28 - 40)
Mean age of onset of NEC (days)	13 days (2 – 26 days)	6.2 (3 - 31)
Days from onset to mean age of laparotomy	6.6 days (3 – 12 days)	2.2 (1 - 5)
Associated significant non-cardiac comorbid conditions (%)	9 (64)	5 (29)
Associated significant cardiac anomalies (%)	7 (50)	6 (35)
Mortality age (%)	10 (71)	5 (29)

PPD - primary peritoneal drainage, SL - salvage laparotomy, PL - primary laparotomy

percentage of lethargy, abdominal mass, respiratory and circulatory collapse, significant thrombocytopenia, significant neutropenia and *Candidal septicemia*, was noticed in the PPD group than in the PL group. Assessment of the radiological parameters across the 4 study groups showed that 96% of medically managed babies had pneumatosis intestinalis versus only 48% in the surgical neonates. Fixed dilated loops (38%) and portal vein air (PVA) (19%) were much higher in the surgically treated group when compared to medically treated group (Fixed dilated loops [16%] and PVA [8%]). The surgically treated group had a 57% incidence of pneumoperitoneum, an entity obviously absent in the medically treated group. Twelve percent of babies in the surgically treated group showed a gasless abdomen as compared to none in the medically treated group. When the radiological parameters were assessed between the PPD and PL groups, a higher percentage of the PPD babies had pneumatosis (69%) and gasless abdomen (16%), than the PL group, which had 16% pneumatosis and 6% gasless abdomen. However, the PL babies had 76% incidence of pneumoperitoneum when compared to only 44% in the PPD group. The PPD group with or without SL, had a very high incidence of septic shock (61%) and mortality (72%) when compared to the PL group (29%) (both septic shock and mortality). The incidence of stomal complications, intestinal strictures, intestinal obstruction, wound infection, and short bowel syndrome, was more or less the same in the PPD + SL and PL groups. In **Table 3**, we assessed the outcome in relation to the extent of bowel involvement in the PPD + SL group versus the PL group, and found that in all 3 types of bowel involvement, the PPD + SL group had a much higher mortality than the PL group. In fact, in the PL group, none of the babies with isolated NEC died. In all the 31 patients undergoing laparotomy, the terminal ileum was the most common site of NEC (58%), followed by the cecum and right colon (26%). In order to study why the primary laparotomy group fared so much better than the SL group, in our study, we compared both these groups according to parameters shown in **Table 4**. It is clear that the PPD + SL group had a much lower mean birth weight and gestational age, as well as a much higher incidence of associated non-cardiac comorbid conditions, and a moderately higher rate of associated cardiac anomalies than the PL group. The mean number of days from onset of NEC to laparotomy is also higher (mean 6.6 days, range, 3-12 days) in the PPD + SL group when compared to the PL group (mean 2.2 days, range1-5 days).

Discussion. Neonatal necrotizing enterocolitis is currently the most catastrophic gastrointestinal surgical emergency in neonates. Medical management is usually successful in those whose ischemic injury has not progressed to full thickness necrosis and perforation. Approximately 50% of babies with NEC will develop advanced disease, which requires surgical intervention.[10] It is reported that although there has been a progressive improvement in the survival of babies with NEC due to earlier diagnosis and advanced neonatal care, the mortality in babies <1000gm is, however, still very high.[11] In infants who require surgical intervention the mortality rate has decreased from 70% to nearly 50%.[12,13] In our study, although the total surgical mortality was 55%, in the PL group it was only 29%. The high mortality was mainly in the PPD group where it was 72%. This can be attributed

to several factors including low birth weight and gestational age, high rate of associated non-cardiac and cardiac comorbid disease, hemodynamic and respiratory instability, persistent metabolic acidosis and significant thrombocytopenia. A platelet count of <100,000/ cu.mm or a rapid fall in platelet count represents a poor prognosis even though it will not predict alone the survival rate or extent of disease.[14] Dykes et al[15] found that the platelet count, blood pH level and associated congenital defects were of prognostic statistical significance in predicting outcome. *Candida sepsis* was the highest (28%) in the PPD group and has been recognized as a contributing factor to mortality.[16,17] Out of 11 babies with *Candida sepsis* in our patients, 7 (64%) died. Since positive candidal cultures are a late finding, a high index of suspicion, and tests other than blood cultures should be carried out so that aggressive antifungal therapy can be started early or empirically.[17] Radiological features in our study have confirmed that pneumatosis is the hall mark of the diagnosis of NEC in the initial medical management phase. Kliegman and Janaroff[18] found a 19-98% rate of pneumatosis in babies with NEC and noticed that it may be absent in up to 14% of those with advanced NEC. Extensive pneumatosis may be present with minimal signs and show a good response to medical therapy[19] as compared to our experience. Fifty-seven percent of our surgical babies had pneumoperitoneum, which was the highest in the PL group (76%) and probably enabled in easy decision making towards laparotomy in this group. In contrast, the PPD group had a higher rate of gasless abdomen than the PL group. A recent study from Saudi Arabia[20] showed gasless abdomen on x-rays to be an indicator of perforation in sick babies with NEC. In our study, PVA was seen in 8% of the medically treated group and 19% of the surgically treated group. None of the medically treated babies with PVA died whereas 7 out of 8 in those undergoing surgery died. Kosloske[21] found PVA to be the best indicator of gangrene. Portal vein air occurs in 10-30% of infants with NEC[22] and has been found to be a poor prognostic sign especially in low birth weight babies, and those with hemodynamic instability.[23] Fixed dilated loops on serial radiographs were present in 16 (38%) of surgically treated and only 4 (16%) of medically treated babies, and in combination with other signs they may be a good indicator for laparotomy. We tried to correlate the extent of disease with mortality, and discovered that in our PL group there were no deaths in those with isolated NEC, with considerably lower mortality even in those with multifocal and pan involvement when compared to the PPD + SL group (**Table 3**). This can again be attributed to the adverse risk factors, as mentioned earlier in the PPD group. In a recent study by Chardot et al,[24] the intestinal lesions in babies <1000gm and NEC were not more severe, though the prognosis of surgical NEC was worse in this group. In the PPD group, the high mortality correlates with the high rate of septic shock, respiratory and hemodynamic instability. In this group, 7 out of 25 babies (28%) were <1000gm and all died. Ricketts and Jerles[25] noticed a significant reduction in survival in babies <1000gm with surgical NEC. Other complications such as stomal retraction, stenosis, wound infection, strictures and short bowel syndrome were more or less similar in the PPD+SL and the PL groups. None of our medically treated babies developed strictures even though this is a well described phenomenon.[26-28] Operated babies in our series showed a stricture rate of 23%, which is consistent with the quoted rate of 9-36%.[29] Similarly, short bowel syndrome manifested in 13% of our postoperative patients. It is well known that 23% of survivors of surgical NEC may develop short bowel syndrome.[29] In NEC, the most frequently affected site is the terminal ileum, which was the case in our series.[30] In fact, Faschling et al[31] noticed a higher mortality rate when the ileum was involved. Diffuse disease or panintestinal involvement was present in 5 (16%) of our operated cases and 80% of these died. A study by Joao et al[32] showed that diffuse involvement in NEC is the most independent predictor of mortality.[32] In the PPD group, the mortality was very high when compared to the PL group in our series. Is PL a better option? There is no consensus regarding this, but as a temporary measure, PPD is well accepted. Rovin et al[7] stated that premature infants with intestinal perforation may improve following PPD and in those with NEC clinical stabilization and recovery of the involved bowel may occur before laparotomy. However, Camberos et al[33] in a recent study of 35 neonates <1500 gms found in that though the survival rates of PPD and PL were comparable; laparotomy allows accurate assessment of the extent of disease, non-viable bowel is removed, recovery is hastened and it is possible for the surgeon to advise parents and make informed decisions. According to them, laparotomy after PPD may be "technically difficult due to scarification and adhesions and this may prolong recuperative phase". Dimmit et al[34] found similar survival rates with PPD or PL but 4 babies with PPD needed SL and all died. They concluded that SL in their small number of patients did not appear beneficial and advised continued medical and supportive management rather than laparotomy. In a meta-analysis of 10 previously reported studies of PPD versus PL, Moss et al[35] found increased survival rate for PL (62.3%) versus PPD (35.6%). However, they felt that by statistical methods it is not possible to overcome the bias in assignment of patients as it is expected to have a much higher mortality in the PPD group. In our study, PPD had a survival of 28% when compared to 35.6 % in this meta-analysis and the PL group had a survival of

71% when compared to 65.3% in the meta-analysis. We agree with the these authors about the bias in the treatment assignment as the PPD group is critically ill and with many adverse risk factors mentioned earlier and therefore considered unfit for laparotomy. The babies who survived after PPD only probably had isolated perforations and those who did not may have had gangrene and extensive bowel involvement.

In conclusion, we feel that PPD should be the initial stabilizing measure in all low birth weight, critically ill babies with perforated NEC but laparotomy should be planned early in those showing signs of ongoing disease, before severe septic shock and coagulopathy prevent any further surgical intervention and this policy may improve the outcome in this group. Larger, fitter babies definitely benefit from PL. Prospective, randomized trials would be more helpful in confirming this observation.

Acknowledgment. The authors would like to thank Ms. Teresita Taruc, for her secretarial assistance, Ms. Khadra Abdulrahman Saber, for her help in retrieving all the medical records in a well organized manner, and the Neonatal Intensive Care Unit Nursing Staff for their cooperation in the identification of cases for this study.

References

1. Kosloske AM. Epidemiology of necrotizing enterocolitis; ***Acta Pediatr Suppl*** 1994; 396: 2-7.
2. Rescorla FJ. Surgical management of pediatric necrotizing enterocolitis. ***Curr Opin Pediatr*** 1995; 7: 335-341.
3. Ein SH, Marshall DG, Gervan D. Peritoneal drainage under local anaesthesia for perforations from necrotizing enterocolitis. ***J Pediatr Surg*** 1977; 12: 963-967.
4. Janik JS, Ein SH. Peritoneal drainage under local anaesthesia for necrotizing enterocolitis: A second look. ***J Pediatr Surg*** 1980; 15: 565-568.
5. Cheu HW, Sukarochana K, Lloyd DA. Peritoneal drainage for necrotizing enterocolitis. ***J Pediatr Surg*** 1988; 23: 557-562.
6. Ein SH, Shandling B, Wesson D, Filler RM. A 13 year experience of peritoneal drainage under local anaesthesia for necrotizing enterocolitis. ***J Pediatr Surg*** 1990; 25: 1034-1037.
7. Rovin JD, Rodgers BM, Burns RC, McGawen ED. The role of peritoneal drainage for intestinal perforation in infants with and without necrotizing enterocolitis. ***J Pediatr Surg*** 1999; 34: 143-147.
8. Walsh MC, Kliegman RM. Necrotising Enterocolitis: Treatment based on staging criteria. ***Pediatr Clin North Am*** 1986; 33: 179-201.
9. Fasoli L, Turi RA, Spitz L, Kiely EM, Drake D, Pierro A. Necrotising Enterocolitis: Extent of disease and surgical treatment. ***J Pediatr Surg*** 1999; 34: 1096-1099.
10. Kosloske AM. Surgery of necrotizing enterocolitis. ***World J Surg*** 1985; 9: 277-284.
11. Synder CL, Rowe MI. Necrotising Enterocolitis. In: O'Neill JA, Rowe MI, Grosfield JL, Fonkalsrud EW, Coran AG, editors. Pediatric Surgery. Philadelphia (PA): WB Saunders Company; 1998. p. 1312-1313.
12. Cikrit D, Mastandrea J, West KW, Schreiner RL, Grosfield JL. Necrotising enterocolitis: Factors affecting mortality in 101 surgical cases. ***Surg*** 1984; 96: 648-658.
13. Engum SA, Grosfield JL. Necrotising Enterocolitis. ***Curr Opin Pediatr*** 1998; 10: 123-130.
14. Ververidis M, Kiely EM, Spitz L, Drake DP, Eaton S, Pierro A. The clinical significance of thrombocytopenia in neonates with necrotizing entero colitis: ***J Pediatr Surg*** 2001; 36: 799-803.
15. Dykes EH, Gilmour WH, Azmy AF. Prediction of outcome following necrotizing enterocolitis in a neonatal surgical unit. ***J Pediatr Surg*** 1985; 20: 3-5.
16. Al-Salem AH, Qaisaruddin S, Abusrair H, Varma KK. Neonatal perforations of the gastrointestinal tract. ***Saudi Med J*** 1998; 19: 141-144.
17. Smith SD, Tagge EP, Miller J, Cheu H, Sukarochana K, Rowe MI. The hidden mortality in surgically treated necrotizing enterocolitis: Fungal sepsis. ***J Pediatr Surg*** 1990; 25: 1030-1033.
18. Kliegman RM, Janaroff AA. Neonatal necrotizing enterocolitis in the absence of pneumatosis. ***Am J Dis Child*** 1982; 136: 618.
19. Albanese CT, Rowe MI. Necrotising Enterocolitis. In: O'Neill JA, Rowe MI, Grosfield JL, Fonkalsrud EW, Coran AG, editors. Pediatric Surgery. Philadelphia (PA): WB Saunders Company; 1998. p. 1305-1306.
20. Hakam Y, Al-Umran K, Darwich M, Khawaja S, Al-Arfaj A. Perforated necrotizing enterocolitis without pneumoperitoneum. ***Middle East Pediatr*** 2003; 8: 6-8.
21. Kosloske AM. Indications for operation in necrotizing enterocolitis revisited. ***J Pediatr Surg*** 1994; 29: 663- 666.
22. Buonomo C. The radiology of necrotizing enterocoloitis. ***Radiol Clin North Am*** 1999; 37: 1187-1196.
23. Molik KA, West KW, Rescorla FJ, Scherer LR, Engum SA, Grosfield JL. Portal venous air: the poor prognosis persists. ***J Pediatr Surg*** 2001; 36: 1143-1145.
24. Chardot C, Rochet JS, Lezeau H, Sen N, Brouillard V, Caeymaex L, et al. Surgical necrotizing enterocolitis: Are intestinal lesions more severe in infants with extremely low birthweight? ***J Pediatr Surg*** 2003; 38: 167-172.
25. Ricketts RR, Jerles ML. Neonatal necrotizing enterocolitis. ***Clin Pediatr*** 1985; 24: 79-82.
26. Bell MJ, Ternberg JL, Askin FB, McAlister W, Shackelford G. Intestinal stricture in necrotizing enterocolitis. ***J Pediatr Surg*** 1976; 11: 319-327.
27. Janik JS, Ein SH, Mancae K. Intestinal Stricture after necrotizing enterocolitis. ***J Pediatr Surg*** 1981; 16: 438-443.
28. Schwartz MZ, Hayden CK, Richardson CJ, Tyson KRT, Lobe T. A prospective evaluation of intestinal stenosis following necrotizing enterocolitis. ***J Pediatr Surg*** 1982; 17: 764-770.
29. Ricketts RR. Necrotising enterocolitis. In: O'Neill JA, Rowe MI, Grosfield JL, Fonkalsrud EW, Coran AG, editors. Pediatric Surgery. Philadelphia (PA): WB Saunders Company; 1998. p. 1314.
30. Balance WA, Dahms BB, Shenker N. Necrotising Enterocolitis. In: O"Neill JA, Rowe MI, Grosfield JL, Fonkalsrud EW, Coran AG, editors. Pediatric Surgery. Philadelphia (PA): WB Saunders Company; 1998. p. 1303.
31. Faschling G, Hollwarth ME, Schmidt B, Saur H. Necrotising enterocolitis in very low birthweight infants. ***Pediatr Surg Int*** 1992; 7: 428-430.
32. Joao CKDS, Ubirajars ICDM, Carla RK. Prognostic factors of mortality in newborns with necrotizing enterocolitis submitted to exploratory laparotomy. ***J Pediatr Surg*** 2001; 36: 482-486.
33. Camberos A, Patel K, Applebaum H. Laparotomy in very small premature infants with necrotizing enterocolitis or focal intestinal perforation: Postoperative outcome. ***J Pediatr Surg*** 2002; 37: 1692-1695.
34. Dimmit RA, Meier AH, Skarsgard ED, Halamet LP, Smith BM, Moss RL. Salvage laparotomy for failure of peritoneal drainage in necrotizing enterocolitis in infants with extremely low birthweight. ***J Pediatr Surg*** 2000; 35: 856-859.
35. Moss RL, Dimmit RA, Henry MCW, Geraghty N, Efran B. A Meta-Analysis of peritoneal drainage versus laparotomy for perforated necrotizing enterocolitis. ***J Pediatr Surg*** 2001; 36: 1210-1213.