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Original Article

Related Factors in Necrotizing Enterocolitis after Gastroschisis Repair

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Abstract ***Background/Objectives:*** **Necrotizing enterocolitis (NEC) has been documented as a complication in infants after repair of gastroschisis. Previous studies showed that the etiology of NEC might be multi-factorial. The aim of this study was to review the experience in the management of neonates with gastroschisis and to identify the risk factors of NEC after gastroschisis repair.**

Methods: **A retrospective case analysis was performed on neonates with gastroschisis treated at the Queen Sirikit National Institute of Child Health between 1998 and 2007. Information data including relevant demography, perioperative data, intravenous parenteral nutrition and enteral feeding were reviewed. The study focused on related factors that might induce NEC after gastroschisis repair. Data were analyzed by the Chi-square and student t-test. Statistically significant difference was considered at the level of a p-value less than 0.05.**

Results: **Four hundred and sixty-six neonates with gastroschisis were treated by definitive operation during the study period. Forty cases died and 11 of these had evidence of NEC (27.5%). Of the total 466 patients, 44 cases (9.4%) developed NEC after gastroschisis repair. The mean of birth weight was significantly different between the NEC and non-NEC groups (2,016.4 ± 658.2g vs. 2,234.2 ± 1,165.5g, p = 0.001). Neonates in the NEC group underwent additional operation due to associated GI anomalies or complications more than the non-NEC group with statistical significance (9/44 vs. 17/422, p <0.001). Regarding sepsis complications, the NEC group had also more common than those of the non-NEC neonates (11/44 vs. 31/422, p = 0.003). There was no difference in associated GI abnormalities between both groups (4/44 vs. 32/422; p = 0.148), except for intestinal atresia. Surprisingly, neonates in the non-NEC group had significantly more early initiating enteral feeding than the NEC group (15.3 ± 11.2 days vs. 18.0 ± 10.5 days; p = 0.007)**

Conclusions: **Low birth weight, underlying compromised bowel, additional operation due to complications and associated GI anomalies especially intestinal atresia were the important predisposing factors for NEC after gastroschisis repair. Delayed initiating enteral feeding is unable to prevent NEC after gastroschisis repair.**

Key words: **closure of abdominal wall defect, gastroschisis, necrotizing enterocolitis**

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Background

The prevalence of gastroschisis has increased significantly in recent years. Although the mortality of gastroschisis has decreased to less than 10 % but the morbidity is still very common; particularly infectious and gastrointestinal complications[1-5]. Intestinal atresia is a common anomaly associated with gastroschisis and is considered as a significant contributor to morbidity and mortality. Necrotizing enterocolitis (NEC) is a well-recognized complication after gastroschisis repair which may cause morbidity and occasional mortality[6-8]. Many authors reported risk factors of NEC after gastroschisis repair and showed that it might be multifactorial[2,6-9]. At our institute, timing of initiating enteral feeding is considered as a risk factor of NEC after gastroschisis repair. Therefore, some surgeons had attempted a delay in initiating enteral feeding postoperatively but NEC remained occurring. The objective of this study was to review the experience in management of neonates with gastroschisis and to identify risk factors of NEC after gastroschisis repair from a single institute for pediatric patients in Thailand.

Methods

Patients

After the proposal was approved by the Institutional Review Board, a retrospective case analysis was performed on neonates with gastroschisis treated at the Queen Sirikit National Institute of Child Health between 1998 and 2007. The patients who had definitive operation from other hospital were excluded from the study. Information data including relevant demographics, perioperative data, intravenous parenteral nutrition, enteral feeding and results of the treatment were reviewed.

Treatment protocol

Infants with gastroschisis were treated by primary closure whenever possible. Patients with major viscera-abdominal disproportion due to large amount of herniated abdominal viscera, marked swelling of the eviscerated bowel with serositis and marked narrowing of the abdominal cavity were treated by staged closure with an artificial sac or silo. This sac was prepared by using Steri-Drape® covering both surfaces of a stockinet tube which was described by Havanonda[2,3] (Fig. 1, 2). The patients who had intestinal infarction, perforation, atresia or stenosis and other complications such as adhesive small bowel obstruction, septic arthritis or wound dehiscence might undergo additional operation for intestinal resection, enterostomy or drainage, etc. All infants with gastroschisis received preoperative intravenous fluid resuscitation, nasogastric (NG) intubation with intermittent suction, preoperative and postoperative antibiotics adjusted by clinical status and postoperative total parenteral nutrition (TPN) in every case.

The patients who suspected NEC status underwent investigations including complete blood count, serum

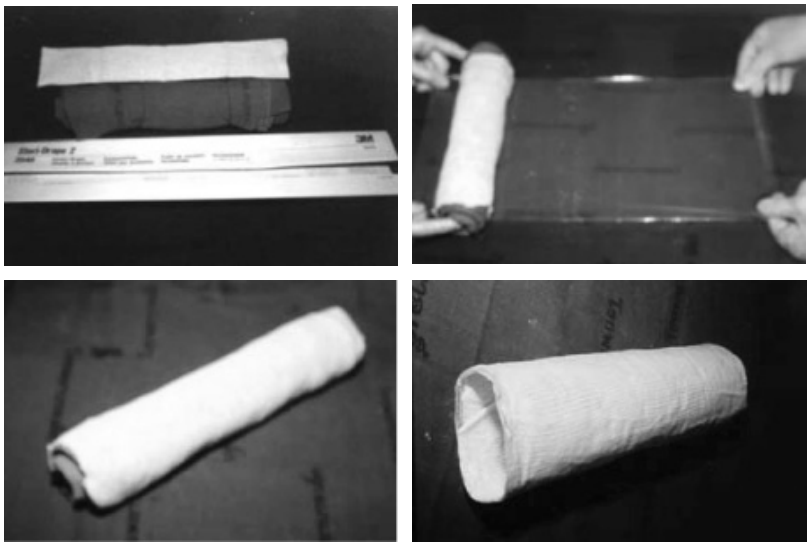

Figure 1 Creation of artificial sac or silo by suing Seri-Drape® covering both surfaces of a stockinette tube.

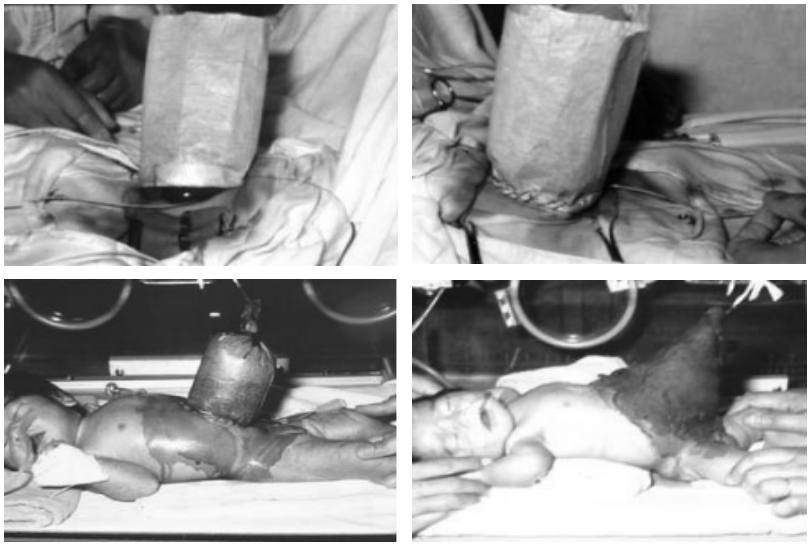

Figure 2 Application of an artificial sac above the abdominal wall defect and continuous suturing between this sac and the defect by No. 2-0, Ethylene.

electrolyte and abdominal roentgenography. Diagnosis and staging of NEC were based on Bell's criteria[10]. Stage I was described as "suspected NEC" and presented with feeding intolerance, lethargy, abdominal distension, bilious vomiting, occult or gross blood in stool and non-specific intestinal dilatation in abdominal roentgenography. Stage II was classified as definite NEC with clinical presentations similar to stage I and association with one of radiological findings such as pneumotosis intestinalis, portal vein gas, persistent rigid bowel loop and peritoneal fluid. Stage III or advanced NEC was categorized with stability of vital signs, evidences of septic shock, peritonitis or pneumoperitoneum in abdominal plain films. After definite diagnosis of NEC was decided, management would be started including NPO approximately 10-14 days, retained NG tube with intermittent suction, intravenous antibiotics, observation of abdominal signs and serial abdominal films.

Statistical analysis

Regarding risk factors related NEC after gastroschisis repair, the data including sex, birth weight, gestational age, modes of operation, associated anomalies, septic complications, timing to start enteral feeding were extracted to analyze by using SPSS for Window version 13.0 with the Chi-square and student t-test. Statistically significant differences were considered at the level of a p-value less than 0.05.

Results

Demographic data

During the study period, 466 neonates with gastroschisis were admitted and treated by definitive operation. Male and female ratio was 236:234 (1:1). Seventy-five patients were born at Rajavithi Hospital (the former name "Women's Hospital"), while the other 391 patients were born at other hospitals. From 1998 to 2007, 89,070 neonates were delivered at Rajavithi Hospital. An incidence of gastroschisis among neonates born at Rajavithi Hospital was about 1: 1,200 live births. The average birth weight was 2,245.5 ± 1,210.8 (range 1,000-3,600 g). Approximately 73% of the patients had the birth weight less than 2,500 g. One half of patients (50%) had mothers who were under 20 years of age during delivery. Most of the patients (74%) were born by vaginal delivery and 69% of maternal pregnancies were primigravida.

Associated congenital anomalies

Additional congenital anomalies were noted in 67 patients (14.4%) and some cases had more than one anomaly. Major associated anomalies included gastro-intestinal (GI), cardiac, genitourinary (GU) and neuro-logical abnormalities. Intestinal atresia was the most common GI anomalies (15 in 36 cases). Jejunoileal, colonic and duodenal atresias were noted in 12, 2 and 1 case, respectively. Common cardiac

defects were patent ductus arteriosus (PDA - 8 cases), atrial septal defect (ASD - 3 cases), and ventricular septal defect (VSD - 1 case). Most of GU anomalies were cryptor-chidism in 11 cases and other minor abnormalities in 4 cases. Neurological anomalies included hydro-cephalus in 3 cases and congenital facial palsy in one case. Seven patients developed intestinal necrosis at the first physical examination due to compression of the eviscerated bowel with a narrow abdominal wall defect during patient transfer. Two of the 7 patients with bowel necrosis were noted to have intestinal perforation.

Modes and results of treatment

Primary closure of abdominal wall defect was performed in 193 patients (41.4%), while staged closure was performed in 273 cases (58.6%) with marked visceroabdominal disproportion. The mean duration of intravenous parenteral nutrition was 16.2 ± 12.7days (ranged 5-50 days) in patients with primary closure, compared to 21.0 ± 16.5days (ranged 7 - 84 days) in the staged operation group ($p < 0.05$). Average length of hospital stay in the primary closure group was shorter than those in the staged operation group (25.5 ± 18.7 days vs. 40.0 ± 26.2 days, $p < 0.05$).

Of the 466 patients, 192 cases (42.3%) developed postoperative complications. The major complications included sepsis (20.7%), NEC (13.2%) and wound infection (10.2%). Forty-seven cases (10%) underwent additional operations due to associated anomalies and complications. Nine of the 47 patients underwent small bowel resection due to intestinal necrosis and required reoperation because of complications following the first operation. Seventeen patients needed reoperations for small bowel resection after complete abdominal closure because of intestinal atresia, anastomotic leaks and enterocutaneous fistula. The remaining 21 cases required other surgical

Table 1 Demographic data of gastroschisis with and without NEC

Patient information	NEC group (n = 44)	Non-NEC group (n = 422)	p-value
Male : female	20 : 24	212 : 210	0.656
Birth weight (g)			
< 1500	3	7	
1500-2000	30	96	
2000-2500	9	196	
2500-3000	2	100	
> 3000	0	23	
Mean	2016.4 ± 658.2	2234.2 ± 1365.5	0.001
Range	1400-2800	1000-3600	
Mean gestational age (w)	36.0 ± 4.8	36.2 ± 6.5	0.701
Range	31-40	24-42	
Mean maternal age at delivery (y)	21.4 ± 6.1	21.0 ± 6.9	0.815
Range	16-38	14-39	
Type of delivery			
Vaginal delivery	43	302	0.065
Cesarean section	1	120	0.137
Birth order of the mother			
First child	42	303	0.071
Second child	1	89	0.182
Third and over	1	30	0.347
Major associated anomalies			
Cardiovascular	0	12	0.526
Gastrointestinal	4*	32	0.138
Neurological	0	4	1.00

*intestinal atresia in all of 4 cases

Table 2 Comparison of results of the treatment between gastroschisis with NEC and non-NEC groups

Information of the treatment	NEC group (n = 44)	Non-NEC group (n = 422)	p-value
Modes of treatment			
Primary closure	10 (22.7%)	170 (40.3%)	0.004
Staged closure	34 (77.3%)	252 (59.7%)	0.023
Additional operations due to major associated GI anomalies and complications	9	17	0.0001
Sepsis	11	31	0.0003
Mortality	11 (25%)	29 (6.9%)	0.0002

Table 3 Comparison of time to the first oral feeding, TPN administration and length of hospital stay in the survivors between NEC and non-NEC groups

Time interval	NEC group (n = 33)	Non-NEC group (n = 393)	p-value
Time to the first oral feeding (days)			
Mean	18.0 ± 10.5	15.3 ± 11.2	0.007
Range	8-52	6-47	
Duration of TPN administration (days)			
Mean	35.4 ± 21.3	19 ± 13.8	0.0001
Range	15-81	(7-149)	
Length of hospital stay (days)			
Mean	51.4 ± 31.5	28.7 ± 25.6	0.0001
Range	26-107	12-159	

procedures for several complications including replacement of artificial sac, exploratory laparotomy and lysis of adhesion, resuturing after wound dehiscence, arthrotomy and drainage, etc.

NEC after gastroschisis repair

Forty-four of the 466 patients (9.4%) developed NEC at the interval 2-6 weeks after gastroschisis repair. NEC occurred after initial enteral feeding in every case. These NEC patients were classified by Bell's criteria[3] with stage I, II and III in 25, 11 and 8 cases, respectively. Comparison of demographic data and results of the treatment of those infants with NEC and without NEC were shown in Table 1. Significant differences were observed in mean birth weight (2,016.4 ± 658.2 vs. 2,234.2 ± 1,365.5, $p = 0.001$) and receiving additional operation due to some GI associated anomalies or complications (9/44 vs. 17/422, $p < 0.001$). Thirty-three patients with NEC (75%) comparison with 103 patients without NEC (24.4%) had birth weight higher than 2,000 gm ($p < 0.001$). Twenty six patients required additional operative procedures after complete gastroschisis repair due to complications or associated anomalies such as intestinal atresia, intestinal necrosis or perforation, anastomotic leak and enterocutaneous fistula. Nine of the 26 patients developed NEC later. The patients in staged closure group had significantly developed NEC higher than those in primary closure group (77.3% vs. 22.7%, $p < 0.001$). Regarding sepsis and mortality, patients with NEC had a higher rate than those without NEC (Table 2).

Of the 466 patients with gastroschisis, 426 cases survived, including 33 cases of NEC group and 422 cases of non-NEC group. Average time to the first oral feeding in NEC group was 18.0 ± 10.5days, while this average time in the non-NEC group was15.3 ± 11.2 days ($p = 0.007$). This study indicated that neonates in non-NEC group had initiating enteral feeding earlier than those in NEC group (Table 3). Average duration of

TPN administration and length of hospital stay (LOS) in the NEC group were significantly longer than those in the non-NEC group also. These longer durations might be partly reflected more complications and complexity of NEC treatment.

Discussion

The incidence of gastroschisis at the Queen Sirikit National Institute of Child Health is increasing in the recent years, compared to the previous study of 1986-1997[2,3]. From the literature review, the incidence of gastroschisis is increasing worldwide for unknown reasons[1-5,11-14]. Some investigators described risk factors of gastroschisis including maternal smoking and using decongestants or aspirin during pregnancy[15-17]. Our results revealed fetal gastroschisis occurring mostly in young mothers with low parity[18]. It seems to be an association between gastroschisis and low birth weight. Theoretically many factors such as nutritional deficits could play a role in the etiology of this condition. Most of the patients with gastroschisis had low birth weight and were borderline premature[15-20]. The present study revealed significantly increased incidence of NEC in low birth weight neonates after gastroschisis repair (Table 1).

Regarding criteria for operative procedures at our institute, patients with perinatal type of gastroschisis who had more stable and less compromised bowel were treated by primary closure. Patients with antenatal type of gastroschisis who had marked swelling of eviscerated bowels due to prolonged exposure to amniotic fluid, marked visceroabdominal disproportion and physiologic derangement, were treated by staged closure. It might be the results that NEC developed after staged closure significantly higher than those after primary closure because of more inflammation, impairing absorption and delayed motility of the intestine. Patients with small abdominal wall defect without serious intestinal abnormalities can safely be managed by primary closure to achieve earlier full enteral feeding and shorten duration of hospital stay.

Infants who required more extensive surgery with possible intestinal resection or ostomy procedure had a high risk of prolonged postoperative ileus and other complications[12,21-23]. Additional operations due to associated anomalies and other septic complications were the important stress factors to develop NEC after gastroschisis repair. From the present study, congenital GI anomalies were not significantly different between the patients with NEC and without NEC groups, except for intestinal atresia. Many investigators reported that gastroschisis association with intestinal atresia was found ranging from 4% to 18% and had a high incidence of morbidity and mortality[6,24,25]. Patients with gastroschisis and intestinal atresia require several operations including invasive treatment for complications. These induce stress condition to the patients and influence developing of NEC.

The concept of early initial enteral feeding is considered as a risk factor of NEC after gastroschisis repair. Some surgeons managed postoperatively gastroschisis repair by attempted delay initial enteral feeding at least 2 weeks. Our present study showed no correlation between early feeding and incidence of NEC after gastroschisis repair. In contrast, many cases with delayed enteral feeding developed NEC higher than those with early oral feeding similar to the study of Jayanthi et al[26]. Walter Nicollet [27] showed improved outcome of infants with gastroschisis by early minimal feeding. Many reports suggested that glucagon-like peptide 2 (GLP-2) is a physiologically relevant hormonal signal linked to the intestinal adaptation associated with enteral nutrition in neonates[27-29]. GLP-2 is a potent intestinal trophic peptide. Enteral feeding was demonstrated to be the primary stimulus for intestinal mucosal growth, producing secretion and increased circulating concentration of GLP-2. Hence, GLP-2 may play a role in the regulation of blood flow for maintenance of intestinal function in conditions of ischemia[26-28]. Additionally, Jayanthi[26] advocated early enteral feeding with maternal expressed breast milk in order to protect the infant from developing NEC after gastroschisis repair.

The present study recommended early enteral feeding by small amount of electrolyte solution and maternal breast milk (trophic feeding) for stimulation of intestinal mucosal growth and bowel function. Early enteral feeding may be protective against NEC after gastroschisis repair.

Conclusions

Etiologies of NEC after gastroschisis repair may be multifactorial. The important related factors in the present study included low birth weight neonates, compromised bowel during gastroschisis repair,

additional operation due to complications and associated GI anomalies, especially intestinal atresia. Delayed enteral feeding could not prevent NEC occurrence post gastroschisis repair.

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Conflict of interest : None

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