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THE DYNAMIC X-RAY OF INTESTINAL PNEUMATOSIS IN NEONATES WHO RECEIVED MULTI-MODAL ENTERAL MEDICATION REGIMEN BOTH IN TREATMENT AND PREVENTION OF NECROTIZING ENTEROCOLITIS.

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ABSTRACT

Despite of history of about 200 years necrotizing enterocolitis is still remains a major concern for neonatologists, pediatric surgeons and gastroenterologists due to its high morbidity and mortality. Diagnosis is based on radiographic evidence of bowel distension, ileus, pneumatosis intestinalis and/or bowel perforation.

Abdominal X-ray have been shown to be useful in helping to monitor the progression of the disease and detecting the presence of necrotizing enterocolitis.

The aim of the study is to determine the effectiveness of the multi-modal 3 component necrotizing enterocolitis prophylaxis per oral scheme (Gentamicin + Nystatin + LactoG synbiotic) in complex treatment of necrotizing enterocolitis and its prevention.

Newborns underwent (n=33) the digital plain-film abdominal radiographs on second day after hospital admission and administration of multi-modal 3 component enteral necrotizing enterocolitis prophylaxis scheme during period of 15th October 2018 to 5th December 2018. The digital x-ray examinations were repeated on 3rd and 5th days in dynamic.

In all 9 newborns with necrotizing enterocolitis on 1st day the intestinal pneumatosis in different manifestations has been revealed by x-ray (24 hours after receive of the multi-modal 3 component enteral necrotizing enterocolitis prophylaxis scheme). On 3rd and 5th days the positive dynamic of intestinal pneumatosis was described by digital x-ray and this corresponded to a positive clinical dynamic.

The results of our study shows that multi-modal 3 component necrotizing enterocolitis prophylaxis per oral scheme (Gentamicin + Nystatin + LactoG synbiotic) has a positive effect on the resolution of process of intestinal damage manifested in the form of intestinal pneumatosis in newborns with necrotizing enterocolitis. Also the multi-modal 3 component necrotizing enterocolitis prophylaxis per oral scheme has a clear effect on the prevention of necrotizing enterocolitis developmental process.

KEYWORDS: *Necrotizing enterocolitis, newborns, intestinal pneumatosis, perforation, abdominal x-ray*

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common serious acquired disease of the gastrointestinal tract in preterm infants [*Lee JS, Polin RA. 2003*]. It is characterized by bowel wall necrosis of various length and depth. Bowel perforation occurs in one third of the affected infants [*Kafetzis DA et al., 2003*]. Although 5 to 25% of cases occur in term infants, it is primarily a disease of preterm infants, with the majority of cases occurring in very low birth weight infants (infants with birth weight < 1500 *g*) [*Kosloske A 1994*]. NEC is categorized into three different stages, with clinical symptoms varying from feeding intolerance to severe cardiovascular compromise, coagulopathy, and peritonitis with or without pneumoperitoneum [*Bell M, et al., 1978*]. The incidence of NEC varies among countries and neonatal centers. It has been reported to affect up to 10% of very low birth weight infants (VLBW) [*Kosloske A 1994*].

The pathogenesis of NEC remains incompletely

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understood. NEC most likely represents a complex interaction of factors causing mucosal injury. It is speculated that NEC occurs with the coincidence of two of the following three pathologic events; intestinal ischemia, colonization of the intestine by pathologic bacteria, and excess protein substrate in the intestinal lumen [*Kosloske A, 1994*; *Khalid Al et al., 2012*]. Bacterial colonization is necessary for the development of NEC [*Kosloske A 1994*]. When compared to term infants, VLBW infants at risk of NEC have abnormal fecal colonization, demonstrate a paucity of normal enteric bacterial species, and have delayed onset of bacterial colonization [*Khalid Al et al., 2012*].

Nosocomial infection is also a frequent complication in VLBW infants. Data from the NICHD Network demonstrated that as many as 25% of these infants have at least one or more positive blood cultures, and 5% have positive cerebrospinal fluid cultures over the course of their hospitalization. Late onset sepsis is associated with an increased risk of death, neonatal morbidity and prolonged hospitalization [*Khalid Al et al., 2012*].

The classic histological finding is coagulation necrosis present in over 90% of specimens [*Ballance W. et al., 1990*].

With NEC, the areas most commonly affected are the terminal ileum and the proximal ascending colon. The pattern of disease may involve a single isolated area or multiple discontinuous lesions. The most common histologic findings are associated with mucosal injury. These include coagulation necrosis of the mucosa with active and chronic inflammation, mucosal ulceration, edema, hemorrhage, and pneumatosis of the submucosa. Advanced disease may result in full-thickness necrosis of the intestinal wall [*Springer S et al., 2017*].

There are several risk factors of NEC such as preterm birth, low birth weight, respiratory distress and acute hypoxia, neonatal anemia, congenital anomalies (especially cardiac anomalies), bacterial colonization, hypoxia/altered intestinal perfusion, polycythemia and formula feeding, blood transfusions [*Claud E et al., 2001; Gephart M. et al., 2012*]. The only consistently described risk factors for NEC are formula feeding, intestinal dysbiosis, low birth weight, and prematurity [*Rose A, Patel R, 2018*]. Low birth weight and prematurity are the most commonly reported risk factors for NEC, with the lowest birth weights and GAs having the highest incidence of NEC [*Samuels N. et al., 2017*].

To assess the severity of NEC and as the standard of practice to diagnose, stage, and treatment of NEC in the NICU, Bell's classification was proposed in 1978 [*Bell MJ, et al., 1978*]. It categorizes the severity of NEC based on clinical and radiographic signs and remains the most widely used tool in early assessment. In recent years, however, this staging criterion has been modified as our understanding of the disease has improved, yet there continues to be controversy about the validity of this staging system at lower gestational ages [*Gordon P et al., 2007*].

According to Bell, NEC is classified into 3 stages (Table) [*Bell M, et al., 1978*]. For descriptive purposes and for disease stratification, the Bell scoring system has been widely utilized, which assesses the degree of NEC severity as mild (Bell stage I), moderate (Bell stage II) or severe (Bell stage III) [*Niño D et al., 2016*]. Severity of NEC plays a key role in both the management and the outcome of affected neonates. Neonates with proven or advanced NEC, categorized as Bell's stage II and III, respectively, are at risk of developing bowel perforation, peritonitis, sepsis and other severe systematic complications including capillary leak syndrome and multi-system organ failure [*Sonntag J. et al., 1998*]. Especially stages 3A and 3B are advanced stages of disease, and are associated with a high mortality, since they lead to intestinal perforation with peritonitis, septic shock and other complications, in a situation with need for surgical interventions. The clinical presentation of NEC is nonspecific, broad and includes variable symptoms which are often non-specific signs of gastrointestinal dysfunction [*Claud E. et al., 2009*]. Diagnosis is based on radiographic evidence as bowel distension, ileus, pneumatosis intestinalis and/or bowel perforation [*Schmolzer G, et al., 2006*].

For instrumental diagnostic the abdominal X-ray have been shown to be useful in helping to monitor the progression of the disease and detecting the presence of NEC. The radiological imaging studies to identify NEC are dilated loops of bowel, pneumatosis intestinalis, portal venous gas and intestinal perforation (Fig. 1. A-D) [*Janssen L. et al., 2018*].

Table

Modified Bell criteria for NEC

Stage	Systemic symptoms	Intestinal symptoms	X-ray – US signs
IA – suspected NEC	Temperature instability, apnea, bradycardia, lethargy.	Increased gastric residuals, mild abdominal distension, emesis, occult blood in stool.	Normal or intestinal dilatation, mild ileus.
IB – suspected NEC	Temperature instability, apnea, bradycardia, lethargy.	Bright red blood from rectum.	Normal or intestinal dilatation, mild ileus.
IIA – proven NEC	Temperature instability, apnea, bradycardia, lethargy.	Bright red blood from rectum, + absent bowel sounds, ± abdominal tenderness.	Intestinal dilatation, ileus, intestinal pneumatosis.
IIB – Proven NEC	Temperature instability, apnea, bradycardia, lethargy, + mild metabolic acidosis, mild thrombocytopenia.	Same as above, + absent bowel sounds, definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass.	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, with or without ascites.
IIIA – advanced NEC (bowel intact)	Same as stage IIB, + hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, neutropenia.	Same as above, + signs of generalized peritonitis, marked tenderness and abdominal distension.	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, + definite ascites.
IIIB – advanced NEC (perforated bowel)	Same as stage IIIA.	Same as stage IIIA.	Intestinal dilatation, ileus, intestinal pneumatosis, + portal vein gas, + definite ascites, + pneumoperitoneum.

Imaging modality in the diagnosis of NEC is historically represented by the plain-film abdominal radiographs which can be performed every 6 hours because of the rapid evolution that may occur in the patient's clinical condition. Radiographic findings have been well described in the literature, ranging from completely unspecific signs, such as a widespread bowel distension, up to more useful signs as wall thickening, fixation of the loops or reduction of intestinal air. X-ray abdomen examination shows a specific pattern only when there is the mucosal damage with pneumatosis of the intestinal wall and pneumoperitoneum [*Esposito, F. et al., 2017*].

Intramural bowel gas, also known as pneumatosis intestinalis, refers to the clinical or radiological finding of gas within the wall of the bowel. Gas in the bowel wall in the neonatal period, whatever its shape, is diagnostic of NEC. Gas tracks along the bowel wall, appearing as either linear, which are usually submucosal, or rounded cystic "bubbly" collections, which are usually subserosal. Where they join, they may outline the circumferenial margin of the bowel, creating rings [*Gharpure V., 2012*].

Pneumoperitoneum describes free gas within the peritoneal cavity, by the disruption of the wall of a hollow viscus. The presence of pneumoperitoneum in newborns with NEC is an already ad-

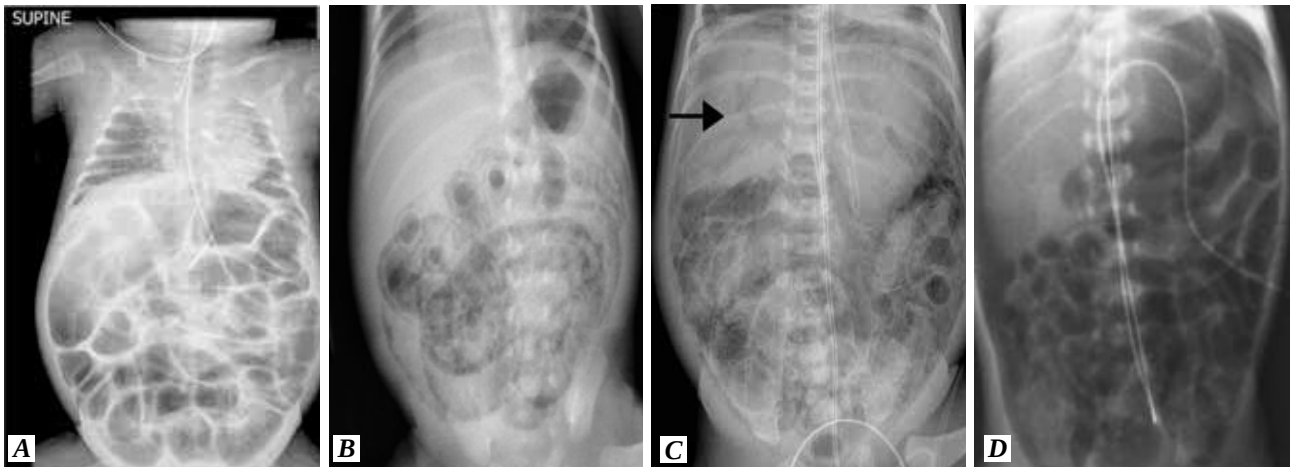

Figure 1. *The radiological abdominal imaging identify NEC presence and its progression.* ***A*** *-Dilated loops of bowel;* ***B*** *- Pneumatosis intestinalis,* ***C*** *- Portal venous gas,* ***D*** *- Pneumoperitoneum*

vanced stage of disease that may precede perforation requires urgent surgical treatment and often leads to a negative outcome [*Anand P. et al., 2016*].

The mainstay of treatment for patients with stage I or II necrotizing enterocolitis is nonoperative management. The initial course of treatment consists of stopping enteral feedings (NPO - ***"nil per os"***), performing nasogastric decompression, intravenous fluids, total parenteral nutrition (TPN) and initiating broad-spectrum antibiotics. Historically, antibiotic coverage has consisted of ampicillin, gentamicin, and either clindamycin or metronidazole, although the specific regimen used should be tailored to the most common nosocomial organisms found in the particular neonatal intensive care unit. Surgical consultation is obtained once NEC is confirmed. [*Springer S et al., 2017*].

A limited number of strategies have proven effective in reducing the prevalence of the most severe stages of NEC, including human milk [*Cristofalo EA et al., 2013*], and potentially probiotics [*Alfaleh K et al., 2011; 2012; Pammi M et al:, 2015; Chang H et al:, 2017*] and bovine Lactoferrin [*Corpeleijn W et al., 2012*]. It is likely that only multifaceted, comprehensive strategies will consistently lead to the prevention of NEC. There is an NEC prevention protocol (multi modal 3 component scheme) which is used at Division of Neonatology of the Department of Pediatrics of the University Clinic in Graz, Austria with minor changes over the last 20 years resulting in a very low incidence of NEC of 1% in children less than 1500 gr. This protocol consisted of oral Gentamicin, oral Nystatin and Probiotic [*Schmolzer G., Urlesberger B et al., 2006*]. No prospective randomized trials with this protocol have been performed due to ethical norms.

The random, double-blind trial was done in 1977 and suggested a policy of treatment with oral gentamicin only for all babies under 1500 g, all babies needing umbilical catheters, and all premature babies with a history of fetal distress, Apgar score less than 7 at 1 or 5 min, or an episode of hypotension and/or hypoxia after birth [*Grylack L et Scanlon J, 1977*].

Since December 2016 the "Austrian protocol" was revised (probiotic L. rhamnosus was replaced with a locally available product: Synbiotic "LactoG", consist of prebiotic - fructooligosaccharide and probiotics containing the following strains: Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium infantis and Lactobacillus acidophilus) and implemented in NICU of "Muratsan" clinical complex of YSMU. Protocol of multi modal 3 component enteral scheme modified and used not only as a prevention for NEC, but also as a component in complex treatment of NEC [*Harutyunyan A et al., 2018*]. The introduction of multimodal 3 component NEC prophylaxis scheme in neonates with necrotizing enterocolitis resulted in significantly reduced NEC associated morbidity and mortality. The improvement of general condition, decrease of morbidity rate and mortality were estimated by clinical and laboratory data compare with the statistical analyses [*Harutyunyan A et al., 2018*]. But for deep research and evidence base data, for the first time, the dynamic X-ray of intestinal pneumatosis in neonates with/or without necrotizing enterocolitis who received multi-modal enteral medication regimen was performed.

MATERIAL AND METHODS.

Ethical Approval

The study was approved by Ethics Committee of IRB (Study reference number 12/SC/0416) and Ethics Committee of YSMU (Study reference No 8, 19.04.2018).

Study design and setting.

The descriptive study performed to reveal the x-ray dynamics of intestinal pneumatosis in newborns at NICU of "Muratsan" clinical complex of Yerevan State Medical University, Republic of Armenia.

The inclusion criteria were newborns admitted to NICU of YSMU who received the multi-modal 3 component enteral NEC prophylaxis scheme for period 15th October 2018 to 5th December 2018.

Newborns divided in 2 groups. First group were newborns with diagnose NEC, who received the multi-modal 3 component enteral NEC prophylaxis scheme as part of the complex treatment of NEC. The second group were newborns who had no clinical diagnose of NEC, but has received the multi-modal 3 component enteral NEC prophylaxis scheme as NEC prevention, because of high risk of NEC development. In both groups the multi-modal 3 component enteral NEC prophylaxis scheme was prescribed at the first day of admittance to NICU.

Figure 1. Figure 2. Figure 3.

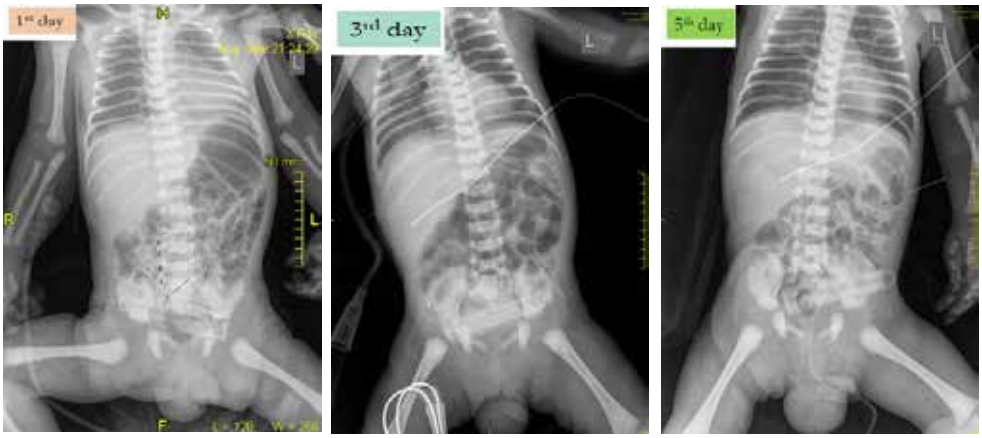

Figure 2. *Abdominal imaging radiographs were done on second day of multi-modal 3 component enteral NEC prophylaxis scheme prescription, and were repeated on 3rd and 5th days*

The plain-film abdominal radiographs examination had been done in all newborns by digital X-ray imaging by "Siemens Iconos R-200" with "Digitizer CR-15X" to reveal intestinal pneumatosis. Abdominal imaging radiographs were done on second day of multi-modal 3 component enteral NEC prophylaxis scheme prescription, and were were repeated on 3rd and 5th days (Fig. 2). All X-ray images were processed by a digital program, with measurements of intestinal wall pneumatosis (Fig. 3). Newborns' data such as weight at birth, gestation age, Apgar and sex were taken into account. The flatulence (metiorism) also described by x-ray.

The x-ray degree of intestinal pneumatosis and flatulence were described by scale of zero to 3+, were zero was the absence of the process and 3+ is the maximum. In the range from zero to three, the initial stages of the process were evaluated by the plus (+), and the average values by two pluses (2+).

Results

33 newborns underwent the digital plain-film abdominal radiographs on second day after hospital admission and administration of multi-modal 3 component enteral NEC prophylaxis scheme during period of 15th October 2018 to 5th December 2018. The digital x-ray examinations were repeated on 3rd and 5th days in dynamic.

9 newborns were clinically diagnosed NEC at admittance at different stages and survived with discharge to pediatric department. In 7 case the NEC stage didn't progress and matched with maximal NEC degree. In 2 cases there were progression of clinical and instrumental findings of NEC after admission but with improvement and good outcome at discharge. In all 9 cases on 1st day the intestinal pneumatosis in different manifestations has been revealed by x-ray (24 hours after receive of the multi-modal 3 component enteral NEC prophylaxis scheme). On 3rd and 5th days the positive dynamic of intestinal pneumatosis was described by digital x-ray and this corresponded to a positive clinical dynamic (Fig. 4 A).

24 newborns (out of 33) were admitted to NICU and have no clinical diagnose of NEC. They received the multi-modal 3 component enteral NEC prophylaxis scheme as NEC prevention. The dynamic x-ray examination revealed the following (Fig. 4 B).

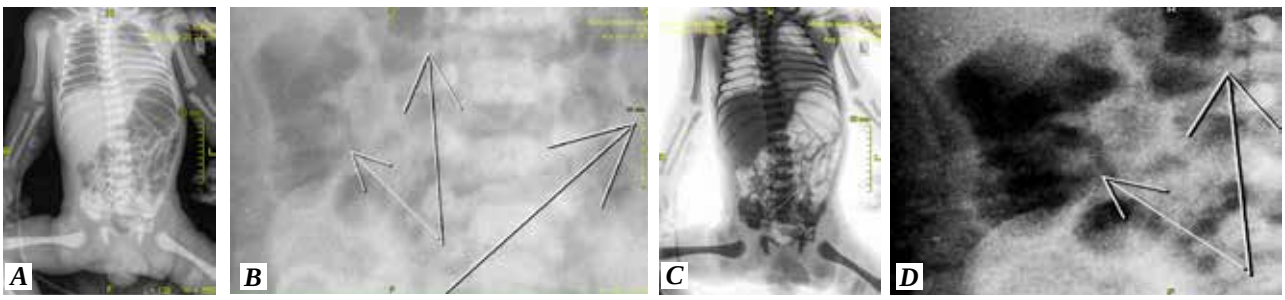

Figure 3. *All X-ray images were processed by a digital program, with measurements of intestinal wall pneumatosis*

- In 14 cases intestinal pneumatosis was absent during all period of x-ray examinations.
- In 9 cases the "mild" intestinal pneumatosis was present on first x-ray examination with positive dynamic on 3rd and 5th days of x-ray. In 3 newborns (out of 9) the "mild" intestinal pneumatosis was present on 3rd day, but was absent on 5th day, as in all 9 cases.
- In 1 case intestinal pneumatosis was absent on first x-ray examination. On 3rd day the intestinal pneumatosis was present in mild form (1+) by x-ray, and then on 5th day it hasn't revealed.
- In all 24 cases on 5th day no intestinal pneumatosis was present on x-ray.

The flatulence (metiorism) was present in 32 newborns on first day of x-ray examination in different degrees of manifestation. In 1 case the flatulence was absent on first x-ray, and developed on 3rd and 5th days.

DISCUSSION

NEC remains a major cause of death for neonates admitted to NICU. The incidence of NEC has increased in the past decades, as the advantages in neonatology and the modern neonatal intensive care unit have led to the increased survival of infants of even smaller birth weight and younger gestational age.

NEC has a multifactorial etiology and the pathogenesis has not fully been elucidated. The classic histological finding is coagulation necrosis present in over 90% of specimens. This finding suggests the importance of ischemia in the pathogenesis of NEC. Inflammation and bacterial overgrowth are also present. There is an assumption that NEC occurs by the interaction of three events: Initially a mucosal injury occurs due to intestinal ischemia, followed by inflammation of the disturbed mucosal integrity with subsequent necrosis of the affected area. The further steps are colonization by pathogenic bacteria and excess protein substrate in the intestinal lumen. Furthermore, the immunologic immaturity of the neonatal gut has been implicated in the development of NEC.

The multi-modal 3 component NEC prophylaxis scheme (Gentamicin + Nystatin + LactoG synbiotic) was applied in NICU of "Muratsan" clinical complex of YSMU. Introduction of multi-modal 3 component NEC prophylaxis enteral scheme has significantly improved the outcome of disease and a reduction of infant mortality not only due to NEC complications but other severe conditions as well. The study has shown that multi-modal 3-component NEC prevention strategy that includes enteral administration of antibiotics, antifungal agent and probiotics used only among newborns with high risk of NEC (birth weight, gestation age and respiratory insufficiency) significantly decreases the number of NEC cases including advance stages, complications and related deaths compared to newborns without multi-modal approach.

The effectiveness of multi-modal 3 component NEC prophylaxis per oral scheme (Gentamicin + Nystatin + LactoG synbiotic) in complex treatment of patients with necrotizing enterocolitis is very high in places, where the early breastfeeding is impossible due to different reasons (donor milk bank absent and etc.).

This is the first descriptive study to reveal the x-ray dynamics of intestinal pneumatosis in new-

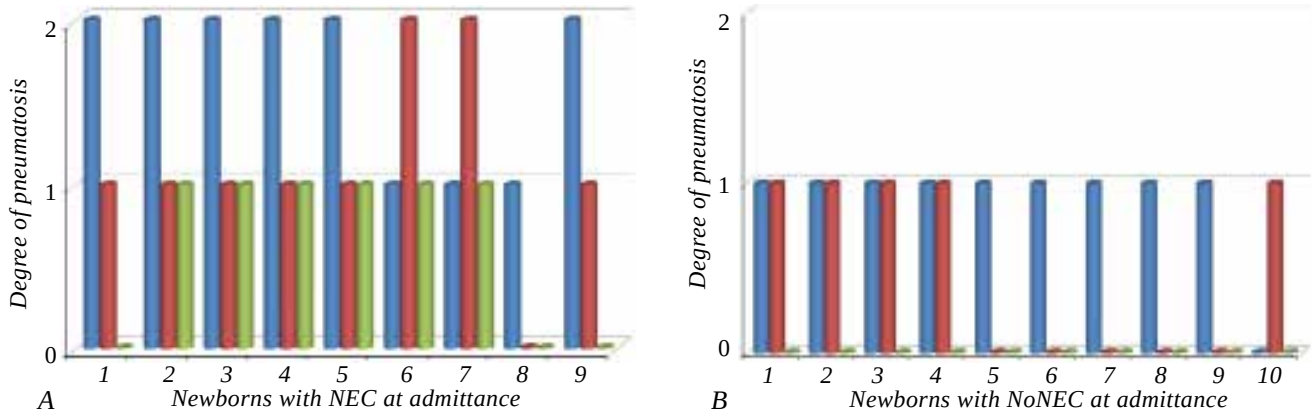

FIGURE 4. *Positive dynamic of intestinal pneumatosis performed on 1st (left bars), 3rd (middle bars) and 5th (right bars) days of x-ray observation at newborns with clinical (A) and no clinical (B) diagnose of NEC.*

borns with necrotizing enterocolitis who received multi-modal 3 component NEC prophylaxis per oral scheme.

Intestinal pneumatosis is the main sign of damage of gut wall. In all 9 newborns with NEC on 1st day the intestinal pneumatosis in different manifestations has been revealed by x-ray (24 hours after receive of the multi-modal 3 component enteral NEC prophylaxis scheme). On 3rd and 5th days the positive dynamic of intestinal pneumatosis was described by digital x-ray and this corresponded to a positive clinical dynamic. In all nine cases with NEC we observed a positive change in intestinal wall by x-ray.

In 24 newborns who admitted to NICU the clinical diagnose of NEC was not present. In 14 cases (out of 24 NoNEC) intestinal pneumatosis was absent during all period of x-ray examinations. In 9 cases (NoNEC) the "mild" intestinal pneumatosis was present on first x-ray examination with positive dynamic on 3rd and 5th days of x-ray. In 3 newborns (out of 9 NoNEC) the "mild" intestinal pneumatosis was present on 3rd day, but was absent on 5th day, as in all 9 cases. In 1 case intestinal pneumatosis was absent on first x-ray examination. On 3rd day the intestinal pneumatosis was present in mild form (1+) by x-ray, and then on 5th day it hasn't revealed. In all 24 cases of NoNEC on 5th day no intestinal pneumatosis was present on x-ray.

It must be mentioned, that we observe reduced mortality and morbidity in NEC cases, after implementation of multi-modal 3 component enteral NEC prophylaxis scheme in NICU of "Muratsan" clinical complex of YSMU science end of 2016 [*Harutyunyan A et al., 2018*]. This study shows positive effect not only in process of NEC development, but also in treatment of necrotizing enterocolitis, where the phenomena of intestinal pneumatosis is the main sign of NEC presents and its degree of bowel damage.

Future research must be conducted to evaluate the effect of multi-modal 3 component enteral NEC prophylaxis scheme both in prevention of NEC development and treatment of NEC. The early stage of NEC with "mild" intestinal pneumatosis must be revealed as soon as it possible by X-ray to control the process of NEC development and its progression.

Conclusion

The results of our study shows that multi-modal 3 component NEC prophylaxis per oral scheme (Gentamicin + Nystatin + LactoG synbiotic) has a positive effect on the resolution of process of intestinal damage manifested in the form of intestinal pneumatosis in newborns with necrotizing enterocolitis. Also the multi-modal 3 component NEC prophylaxis per oral scheme has a clear effect on the prevention of NEC developmental process.

REFERENCES

1. *Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T.* Cochrane Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2011; 3: CD005496.
2. *Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T*. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2011; 3: CD005496.
3. *Anand P, Shailendra S, Vipin G, Rajesh V.* Conservative Management of pneumoperitoneum in Necrotizing Enterocolitis - Is it Possible? J Neonatal Surg. 2016; 5(2): 12.
4. *Ballance WA, Dahms BB, Shenker N, Kliegman RM.* Pathology of neonatal necrotizing enterocolitis: a ten-year experience. J Pediatr. 1990; 117(1 Pt 2): S6-S13.
5. *Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L., et al.* Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978; 187(1): 1-7.
6. *Chang HY, Chen JH, Chang JH, Lin HC, Lin CY, Peng CC.* Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: An updated meta-analysis. PloS One. 2017; 12(2): e0171579.
7. *Claud EC, Keegan KP, Brulc JM., et al.* Bacterial community structure and functional contributions to emergence of health or necrotizing enterocolitis in preterm infants. Microbiome. 2013; 1(1): 20.

8. *Claud EC, Walker WA.* Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. FASEB J. 2001; 15(8): 1398-1403.
9. *Corpeleijn WE, Kouwenhoven SMP, Paap MC, van Vliet I, Scheerder I, Muizer Y., et al*. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. Neonatology. 2012; 102(4): 276-281.
10. *Esposito F, Mamone R, Di Serafino M, Mercogliano C, Vitale V., et al.* Diagnostic imaging features of necrotizing enterocolitis: a narrative review. Quantitative Imaging in Medicine and Surgery. 2017; 7(3): 336-344.
11. *Gephart SM, McGrath JM, Effken JA, Halpern MD.* Necrotizing enterocolitis risk: state of the science. Adv Neonatal Care. 2012; 12(2): 77-87.
12. *Gharpure V*. Neonatal necrotizing enterocolitis. J Neonatal Surgery. 2012; 1: 34.
13. *Gordon PV, Swanson JR, Attridge JT., et al.* Emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell's criteria? J Perinatol. 2007; 27(11): 661-671.
14. *Grylack L, Scanlon JW.* Prevention of necrotising enterocolitis with gentamicin. Lancet. 1977. 506.
15. *Harutyunyan AS, Hovhannisyan MG, Badalyan AR, Muradyan AA, Babloyan AS.* The introduction and results of multi-modal 3 component prophylaxis scheme both in prevention and treatment of necrotizing enterocolitis in newborns. The New Armenian Medical Journal. 2018; 12(4): 4-17.
16. *Janssen Lok M, Miyake H, Hock A, Daneman A, Pierro A, Offringa M.* Value of abdominal ultrasound in management of necrotizing enterocolitis: a systematic review and meta-analysis. Pediatr Surg Int. 2018; 34(6): 589-612.
17. *Kafetzis DA, Skevaki C, Costalos C.* Neonatal necrotizing enterocolitis: an overview. Curr Opin Infect Dis. 2003; 16(4): 349-355.
18. *Kosloske AM*. Epidemiology of necrotizing enterocolitis. Acta Paediatr Suppl. 1994; 396: 2-7.
19. *Lee JS, Polin RA*. Treatment and prevention of necrotizing enterocolitis. Semin Neonatol 2003; 8: 449-459.
20. *Niño DF, Sodhi CP, Hackam DJ*. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. Nat Rev Gastroenterol Hepatol. 2016; 13(10): 590-600.
21. *Pammi M, Abrams SA.* Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2015; 2: CD007137.
22. *Rose AT, Patel RM*. A critical analysis of risk factors for necrotizing enterocolitis. Semin Fetal Neonatal Med. 2018; 23(6): 374-379.
23. *Samuels N, van de Graaf RA, de Jonge RCJ., et al*. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. BMC Pediatr. 2017; 17(1): 105.
24. *Schmolzer G, Urlesberger B, Haim M, Kutschera J, Pichler G., et al*. Multi-modal approach to prophylaxis of necrotizing enterocolitis: clinical report and review of literature. Ped Surgery Int. 2006; 22: 573-580.
25. *Sonntag J, Wagner MH, Waldschmidt J., et al.* Multisystem organ failure and capillary leak syndrome in severe necrotizing enterocolitis of very low birth weight infants. J Pediatr Surg. 1998; 33(3): 481-484.
26. *Springer SC, JD, MD, MSc, MBA, FAAP, Annibale DJ, MD*. Which histologic findings are characteristic of necrotizing enterocolitis? Necrotizing enterocolitis; Pediatrics: Cardiac Disease and Critical Care Medicine; Medscape. 2017.
27. *Springer SC*, JD, MD, MSc, MBA, FAAP. Necrotizing enterocolitis; Pediatrics: Cardiac Disease and Critical Care Medicine; Medscape. 2016.