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SHORT COMMUNICATION

Enteral nutrition strategies in high-risk newborns

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ABSTRACT

Necrotizing enterocolitis (NEC) is one of the most devastating intestinal disorders in neonates, yet the pathophysiology remains incompletely understood. Prematurity, bacterial dysmicrobia, intestinal ischemia and enteral nutrition are considered to be the fundamental risk factors for the development of necrotizing enterocolitis. Various feeding practices are being studied with the aim to find the best approach to protect infants from the necrotizing enterocolitis. In the group of high-risk neonates, the common practice of delayed introduction of enteral feeding has long been considered as a good rationale. However, in recent years, the importance of enteral nutrition has been extensively studied and it is suggested that minimal enteral feeding may play a beneficial role in the prevention of the disease. Studies proved that the absence of enteral nutrition is associated with intestinal mucosal atrophy, diminished intestinal growth, delayed maturation of intestinal enzymes and increased permeability and bacterial translocation. Minimal enteral feeding can on the other hand stimulate the development of the immature gastrointestinal tract and reduce systemic inflammatory responses by promoting proliferation of gut microbial diversity.

KEY WORDS: necrotizing enterocolitis; minimal enteral feeding; hypoxia-ischaemia; inflammation; human milk; dysmicrobia

Introduction

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is an acute inflammatory disease of the gastrointestinal tract that primarily affects premature infants. It is characterized by coagulative transmural necrosis of the intestine with the high risk for the perforation and acute peritonitis. The inflammation can progress to systemic infection with multiorgan failure and death. The most common localization is distal ileum, caecum and proximal colon. Despite the advances in clinical research, the mean prevalence is 5 to 10% among very low birth weight infants and remains unchanged for past years. The associated morbidity and mortality are high. In 20% of cases, the surgical intervention is needed. Extended intestinal resection predisposes infant to the development of short bowel syndrome leading to the feeding intolerance and prolonged need for parenteral nutrition. Infants with severe NEC cases are endangered with neurodevelopmental delays. An estimated mortality of 20 to 30% makes necrotizing enterocolitis one of the most devastating and feared disorders in neonates (Neu & Walker, 2011; Shulhan *et al.,* 2017).

The pathophysiology

The pathophysiology of the necrotizing enterocolitis is incompletely understood. Epidemiologic observations strongly suggest a multifactorial cause. The combination of prematurity, microbial dysbiosis, ischaemia and enteral feeding is considered to be responsible for the development of the necrotizing enterocolitis. While prematurity appears to be the most consistent factor, the role of the microbial colonization, ischaemia and enteral feeding in the pathogenesis of the disease is being extensively studied (Neu & Walker, 2011; Shulhan *et al.,* 2017).

Prematurity

90% of NEC cases occur in babies born before 32nd week of gestation and the incidence increases with the decreasing gestational age and birth weight. Immature gut functions

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(such as motility, digestion, absorption), decreased structural integrity of the gut and underdeveloped immune defenses predispose the preterm infant to an enhanced risk of intestinal injury. Increased expression of toll-like receptors 4 in premature infants lead to an excessive and inappropriate inflammatory response. Premature neonates are more often endangered by respiratory and circulatory instability, use of medications that can cause intestinal mucosal injury (H_2 blockers, cyklooxygenase inhibitors etc.), prolonged antibiotic use or formula feeding. All of these factors can potentiate the development of local ischaemia and following inflammation leading to the development of NEC.

Microbiome

Microbial colonization of the intestine is shaped by various factors such as formula feeding, caesarean section, prolonged hospital stay or exposure to the antibiotic therapy. The optimal microbiome plays a significant role in the protection of the newborn´s gut. Commensal bacteria play a symbiotic role in the intestine by influencing the immune responses, gut maturation and function. Disruption of the commensal flora may lead to the overgrowth of pathogenic bacteria with potential risk of bacterial translocation into the mucosa triggering the immune response and local inflammation of the bowel.

Hypoxia/ischaemia/reperfusion injury

Adequate blood flow is important to maintain the homeostasis within the intestine. It supplies the intestine with the oxygen and nutrients that are needed to generate energy to protect the integrity of the gut wall and perform digestive and absorptive processes. When the metabolic requirements of epithelial cells are not met due to the diminished splanchnic blood supply, the gut is endangered with local ischaemia and necrosis. Necrotic epithelial lining is susceptible to bacterial invasion triggering the inflammatory process. The exact role of intestinal ischaemia in the pathogenesis of NEC is still unknown, but it is thought that hypoperfusion and subsequent reperfusion occurring in response to hypoxia may contribute to bowel injury, immune activation and uncontrolled inflammation (Nowicki, 1990; Shah, 2016; Strodtbeck, 2003; Young, Kingma, Neu, 2011).

Enteral feeding

Most of the infants who developed NEC had been enterally fed. Experimental NEC does not occur in sterile bowel. While premature gastrointestinal tract is structurally and functionally deficient, aggressive feeding that excesses the bowel capacity may lead to the stasis of intraluminal content and bowel dilatation with the risk of bacterial overgrowth. Enteral feeding can also cause an alteration in the blood flow leading to transient hypoperfusion of the intestine after feeding. Several studies have indicated that formula feeding, compared to mother's milk, increases the incidence of NEC. Using hyperosmolar solutions can contribute to the initiation of intestinal injury (Caplan, 2014).

Feeding strategies

Several enteral feeding strategies have been studied to prevent the development of necrotizing enterocolitis. Despite the progressing research, currently, there is no clear consensus among neonatologists on feeding practices in preterm infants, especially in the high-risk group of neonates. There are wide variations not only between the countries but also between individual hospitals. Questions on when to initiate the enteral feeding, how fast to advance individual doses, whether to use human milk or formula and using of fortification have certainly been asked by every doctor working on neonatal intensive care unit.

The group of high-risk infants

In this article, we will focus on newborns that are endangered by the splanchnic hypoperfusion and are therefore considered high-risk in terms of feeding intolerance and the development of the necrotizing enterocolitis. This group of infants does not only involve premature infants but also term infants that undergo splanchnic hypoxia.

Intestinal hypoperfusion may be evocated by the activation of the diving seal reflex that is responsible for cardiac output redistribution away from the splanchnic organs to preserve blood flow for the vital organs such as heart, brain and adrenal glands. In this situation of adrenal axis stimulation, the intestine is suffering from hypoperfusion and is prone to developing local hypoxia/ischaemia. Ischaemia triggers the inflammatory cascade making the intestinal wall susceptible to bacterial invasion especially after the exposure of intraluminal substrate that might worsen the splanchnic hypoperfusion. Many perinatal stresses such as respiratory distress, asphyxia, hypothermia, hemodynamic instability with hypotension and the need for vasoactive agents, congenital heart defects (for example hemodynamically significant persistent ductus arteriosus) severe anemia, polycythemia, septic shock or umbilical vessel catheterization may lead to the blood flow perturbations and splanchnic hypo perfusion (Young *et al.,* 2011)

Among these high-risk infants, we may also comprise intrauterine growth restricted neonates especially if associated with reversed end diastolic flow velocities in antenatal Doppler studies of the umbilical artery (Karagianni *et al.,* 2010). Delayed introduction of enteral feedings in this group of high-risk newborns have therefore seemed like a good rationale and have been practiced in many neonatal intensive care units.

Delayed introduction of enteral nutrition

However, more recent data suggest that withholding enteral feedings with the need of prolonged total parenteral nutrition may be a dangerous practice. The absence of enteral nutrition creates a state luminal starvation. The consequence of disuse and enterocyte starvation leads to the atrophy of intestinal mucosa, villi flattening, diminished intestinal growth, delayed maturation of intestinal enzymes and altered micro-biome. As this phase progress, the gut loses its integrity and permeability of the

intestinal wall increases. This creates a potential risk for bacterial translocation. Prolonged duration of intravenous nutrition increases the risk of infectious complications and delays the hospital discharge (Strodtbeck, 2003).

Minimal enteral feeding

The importance of enteral nutrition has been extensively studied and it is suggested that enteral feeding may play a beneficial role in the disease. It is recognized that fetus constantly swallows amniotic fluid that contains a variety of growth factors and substances that stimulates the development of gut. At birth, the gastrointestinal tract of the newborn is an experienced organ that is physiologically active. Withholding enteral feed creates an abnormal physiologic situation that predisposes the newborn to the negative consequence of enteral starvation. A current alternative attempt at the prevention of necrotizing enterocolitis is to provide minimal enteral feeding to high-risk newborns instead of leaving them no feeding through mouth. This strategy enhances the maturation of the gastrointestinal tract and stimulates the endocrine function by secretion of hormones such as enteroglucagon, gastrin and gastric-inhibiting polypeptide. It also reduces systemic inflammatory responses by promoting proliferation of gut microbial diversity. The bacterial overgrowth might be suppressed by stimulating the peristaltic activity in response to enteral feeding. Animal studies have shown a 2 to 3 fold increase in intestinal mucosa mass with early enteral feeding. This might be mediated by various growth factors contained in human milk. In minimal enteral feeding (MEN) or otherwise called "gut priming", small amounts of feed are given to neonates. Volumes from 10 to 15 ml/kg/day are usually used for 5 to 7 days without advancing to enhance the maturity of the gastrointestinal tract and to facilitate smooth transition to enteral feeding (Mishra *et al.,* 2008).

Human milk vs. formula feeding

Human milk should be preferred as it a substance uniquely suited to the human infant with its ideal nutritional composition. Moreover, it contains various bioactive substances that cannot be found in commercial formulas. There are many immunological factors such as secretory immunoglobulin A, cytokines, chemokines, lymphocytes and stem cells that play very important anti-inflammatory function (Ballard & Morrow, 2013). It also contains various growth factors that promote the structural growth and maturation of the intestine. By lowering the gastric pH and oligosaccharides, human milk stimulates the growth of probiotic bacteria. In case mother's milk cannot be obtained, the donor milk may be a good alternative (Ramani & Ambalavanan, 2013).

Clinical studies

Several clinical studies have been evaluating the strategy of enteral nutrition of high-risk newborns. The first data demonstrating a beneficial effect of minimal enteral nutrition in premature neonates were published in 1988 in the prospective randomized trial done by Dunn *et al.* (Dunn *et al.,* 1988). Total of 39 infants with average birth weight of 930–990 g were divided into 2 groups. The minimal enteral feeding group received 15 to 20 ml/kg of enteral nutrition starting at 48 hours of age. The control group received total parenteral nutrition until 9 days of life. This study showed sooner achievement of full enteral feedings in MEN group, with less need for phototherapy and lower level of osteopenia without increasing the incidence of necrotizing enterocolitis. Cochrane meta-analysis done by Tyson *et al.* in 1997 showed overall reduction in mean of days to full feeding and days of hospital stay among infants receiving minimal enteral nutrition compared to the infants without enteral feeds. No significant increase in the incidence of necrotizing enterocolitis appeared (Tyson & Kennedy, 2005).

The current Cochrane systematic review published in 2013 by Morgan *et al.* (Morgan *et al.,* 2013) evaluated the effect of MEN on feeding tolerance, growth and development, incidence of NEC and mortality. Nine trials with 745 preterm infants were eligible for inclusion. Most of the infants were very low birth weight (VLBW), few participants weighted less than 1000 g. Randomized or quash randomized trials that assessed the effect of MEN with volumes up to 24 ml/kg/days started within the first 3 days after birth and continued at least for one week versus enteral fasting for comparable period were selected. Although some trials reported that trophic feeding reduce the time to achieve full feeds, meta-analysis showed no statistically significant difference between enteral feeding group and fasting group. There was also no difference in terms of the duration of hospital stay. Providing minimal enteral nutrition did not lead to an increased risk of necrotizing enterocolitis or higher mortality in very preterm or VLBW infant.

Karagianni *et al.* in their randomized, non-blinded pilot trial targeted the group of infants with intrauterine growth restriction and abnormal antenatal Doppler results (Karagianni *et al.,* 2010). During the period of 4 years, 81 preterm hypotrophic infants (27 to 34 weeks of gestation) were included in the study. The patients were divided into two groups, the infants from the first group received early minimal enteral feeding while the second group infants received delayed minimal enteral feeding (range 6 to 14 days). No significant difference in the feeding tolerance and in the incidence of NEC was observed. The relative risk for NEC was 1.538 higher in the first group.

In term neonates undergoing the therapeutic hypothermia due to severe asphyxia withholding enteral feeding has been practiced almost universally to prevent necrotizing enterocolitis due to above mentioned risks. However, in recent years, the trend is changing. In 2014, United Kingdom survey found that 79% of 42 units withheld enteral feeding during therapeutic hibernation. In 2017, a similar survey of 49 responding units reported decrease to 41%. Only few small studies have been evaluating the impact of enteral feeding during therapeutic hypothermia. The retrospective study of 34 infants in

the USA found lower inflammatory cytokine concentrations and reduction in days of parenteral nutrition and hospital stay in the enteral feeding group compered to nothing by mouth (NPO) group. Similar retrospective cohort study of 85 infants compared infants in the UK, where 33% infants were fed, to Sweden where 91% of neonates received milk during therapeutic hypothermia. There was no difference found in clinical outcome in both groups, no NEC case appeared (Ojha *et al.,* 2019). Further research with sizable group of infants is needed to provide nutritional guidelines in this particular group of infants.

Conclusion

The necrotizing enterocolitis is one of the most common gastrointestinal emergencies in neonatal age and although early recognition and adequate treatment improves the overall outcome, the morbidity and mortality stay high. Therefore, the preventive approach such as adequate enteral feeding strategy becomes the area of major interest. For many years, delayed introduction of enteral feeding was a part of routine practice in the high-risk group of infants.

However, more recent data indicate that prolonged period of parenteral nutrition is harmful due to its infectious and metabolic complications. Minimal enteral nutrition, on the other hand, appears as a safe and benefitial alternative to complete fasting without increasing the incidence of NEC. Further research is needed to introduce the relevant guidelines for clinical practice.

REFERENCES

Neu J and Walker WA. (2011). Necrotizing enterocolitis. *N Engl J Med* **364**(3): 255–264.

Shulhan J, Dicken B, Hartling L, Larsen BM. (2017). Current knowledge of necrotizing enterocolitis in preterm infants and the impact of different types of enteral nutrition products. *Adv Nutr* **8**(1): 80–91.

Strodtbeck F. (2003). The pathophysiology of prolonged periods of no enteral nutrition or nothing by mouth. *Newborn and Infant Nursing Reviews* **3**: 47–54.

Young Ch, Kingma S, Neu J. (2011). Ischemia-reperfusion and neonatal intestinal injury. *J Pediatr* **158**: e25–28.

Caplan MS. (2014). Necrotizing enterocolitis in preterm infants is related to enteral feeding, but the mechanisms remain uncertain and have changed over time. *Curr Pediatr Rep* **2**: 241–247.

Karagianni P, Briana DD, Mitsiakos G, Elias A, Theodoridis T, Chatziioannidis E, Kyriakidou M, Nikolaidis N. (2010). Early versus delayed minimal enteral feeding and risk for necrotizing enterocolitis in preterm growth-restricted infants with abnormal antenatal doppler results. *Am J Perinatol* **27**(5): 367–373.

Mishra S, Agarwal R, Jeevasankar M, Ashok KD, Vinod KP. (2008). Minimal enteral nutrition. *Indian J Pediatr* **75**(3): 267–269.

Ramani M and Ambalavanan N. (2013). Feeding practices and necrotizing enterocolitis. *Clin Perinatol* **40**(1): 1–10.

Dunn L, Hulman S, Weiner J, Kliegman R. (1988). Beneficial effects of early hypo caloric enteral feeding on neonatal gastrointestinal function: Preliminary report of a randomized trial. *J Pediatr* **112**: 622–629.

Tyson JE and Kennedy KA. (2005). Trophic feedings for parenterally fed infants. *The Cochrane Database of Systematic Reviews.* **3**: CD000504.

Morgan J, Bombell S, McGuire W. (2013). Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. *Cochrane Database of Systematic Review* **3**: CD000504.

Ojha S, Dorling J, Battersby C, Longford N, Gale Ch. (2019). Optimising nutrition during therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed* **104**: F230–F231.

Ballard O and Morrow AL. (2013). Human milk composition: nutrients and bioactive factors. *Pediatr Clin North Am* **60**(1): 49–74.

Shah Y. (2016). The role of hypoxia in intestinal inflammation. *Mol Cell Pediatr* **3**(1): 1.

Nowicki P. (1990). Instestinal ischemia and necrotizing enterocolitis. *J Pediatr* **117**(1): S14–S19.