NECROTIZING ENTEROCOLITIS, PATHOGENESIS AND THE PROTECTOR EFFECT OF PRENATAL CORTICOSTEROIDS

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Necrotizing enterocolitis is the most frequently occurring gastrointestinal disorder in premature neonates.

Animal models of necrotizing enterocolitis and prenatal administration of cortisone have demonstrated that cortisone may accelerate maturation of the mucosal barrier, therefore reducing the incidence of this gastrointestinal disorder.

The authors present a review of the literature of the most important risk factors associated with necrotizing enterocolitis, such as inflammatory gastrointestinal mediators, enteral feeding and bacterial colonization, and immaturity of the gastrointestinal barrier, and we emphasize the necessity for additional studies to explore the prenatal administration of cortisone as a preventive strategy for necrotizing enterocolitis.

DESCRIPTORS: Necrotizing enterocolitis. Neonate. Prematurity. Cortisone therapy. Physiopathology.

INTRODUCTION

Necrotizing enterocolitis (NEC) is a common neonatal gastrointestinal disease that affects approximately 11% of premature neonates weighing less than 1500 g[1]. The average mortality is 20% to 40%, and survivors after either medical or surgical therapy can present with failure to thrive, feeding abnormalities, diarrhea, or bowel obstruction[2].

The etiology of NEC is multifactorial, and the most important risk factors are prematurity, hypoxia and/or intestinal ischemia, and enteral feeding and gastrointestinal bacteria colonization[3].

The association of such risk factors might trigger a local inflammatory cascade with release of inflammatory mediators, resulting in NEC[4]. Alternatively, an imbalance between local inflammatory mediators and an immature local defense could result in NEC defense.

Early signs of NEC are indistinguishable from sepsis neonatorum. The signs and symptoms are quite variable, ranging from feeding intolerance to evidence of sepsis, shock, peritonitis, and death. The usual presentation includes abdominal distension, gastric residuals, bilious vomiting, and bloody stools. Lethargy, apnea, and hypoperfusion also may be a prominent feature. Physical findings found on serial examination comprise progressive abdominal tenderness, muscular guarding, and abdominal wall erythema. The presence of an abdominal mass may indicate localized perforation or progressive peritoneal irritation. However, these physical findings may be minimal and misleading, even in infants with progressive disease leading to perforation[2].

Since prematurity is the most important risk factor associated with NEC, possible therapeutic approaches that promote maturation of the gastrointestinal mucosal barrier, such as the prenatal administration of corticosteroids, have been explored.

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1. INTESTINAL INFLAMMATORY MEDIATORS

Animal models of bowel necrosis have been established by injection of platelet-activating factor (PAF)[5,6], endotoxin (bacterial lipopolysaccharide or LPS)[5,7], and tumor necrosis factor (TNF)[8]. PAF has been implicated as the most important mediator in the pathophysiology of NEC[5,].

Platelet-activating factor is a endogenous phospholipid mediator produced by inflammatory cells, platelets, endothelial cells, and some bacteria, such as *Escherichia coli*[10-14]. PAF has a short half-life in the circulation, due to the high plasma and tissue PAF-degrading enzyme acetylhydrolase (PAF-AH) activity[15,16], which rapidly degrades PAF into the biologically inert lyso-PAF[17].

Mesenteric or systemic administration of PAF in rats induces intestinal injury similar to NEC[5]. On the other hand, the administration of PAF receptor antagonists in animal models of NEC induced by hypoxia, endotoxin, and PAF prevented intestinal mucosal injury[7,8,18].

Considerable evidence indicates that the altered regulation of PAF-AH may play a role in the occurrence of NEC because:

1) PAF-AH activity is decreased in neonates and approaches adult enzyme activity only after 6 weeks of life[19],
2) PAF-AH activity is deficient in sick neonates with NEC[20],
3) PAF-AH activity can be demonstrated in breast milk (formula has none), and use of breast milk reduces the incidence of NEC[21,20],
4) The administration of PAF-AH in animal models of NEC induced by hypoxia reduced the incidence of NEC[23].

Cundell et al.[24] have demonstrated that the PAF receptor is an important determinant of bacterial (Streptococcus) adhesion and invasion into endothelium and epithelium. Mackendrick et al.[25] have found that neonates fed enterally had higher levels of PAF and endotoxin after feeding than before feeding.

The cytotoxic effect of PAF is most likely due to reactive oxygen radical formation[9,26-29], and its prolonged effect seems to be due to its ability to induce TNF formation by intestine and liver[30] as well as to stimulate its own production[31].

Xanthine oxidase (XO)[29,32], an enzyme in intestinal tissue, appears to be the major source of free radicals in reoxygenated tissue. Reperfusion of the tissue supplies molecular oxygen, which results in a burst of superoxide radical production that damages intestinal tissue by peroxidation of unsaturated lipids within the cellular and mitochondrial membranes.

PAF-induced bowel injury is not only associated with production of oxygen-derived free radicals, but also with neutrophil margination and activation and capillary leakage[33]. The importance of neutrophil cells in initiating the intestinal injury has been demonstrated in leukopenic mice and rats, which were relatively protected from PAF-induced bowel injury[34,35].

Nitric oxide (NO) has been demonstrated to be a protective modulator for the intestinal mucosa[36-39]. Nitric oxide has been described as an endothelium-derived relaxing factor that promotes vasodilation and microvascular integrity, inhibits leukocyte adhesion and activation, and scavenges oxygen radicals.

Nitric oxide synthase is the enzyme responsible for NO production[40]. Animal models of bowel injury induced by ischemia-reperfusion[41,42], endotoxin[43], and PAF[44] have shown that intestinal injury is markedly exacerbated by the concomitant inhibition of the NO synthase. The results of these studies suggest that an imbalance between endogenous NO and PAF production may be the factor responsible for intestinal mucosal injury.

2. ENTERAL FEEDING AND BACTERIA COLONIZATION

Enteral feeding and the pattern of intestinal colonization and bacteria adherence are risk factors for developing NEC and therefore have been studied by several researchers[45-52].

The pattern of intestinal colonization varies according to the type of enteral feeding that the neonate is receiving[48]. Breast feeding causes gastrointestinal colonization predominantly by bifidobacteria (Gram-positive bacteria), which control the growth of Gram-negative bacteria[48-52]. In contrast, formula-fed neonates are colonized predominantly by coliforms, enterococci, and Bacteroides spp.[50].

There are important differences between Gram-positive and Gram-negative bacteria regarding intestinal carbohydrate metabolism[53]. The fermentation of lactose by Gram-positive bacteria yields lactic acid, which can be readily absorbed from the intestinal tract. Conversely, Gram-negative bacteria ferment lactose into hydrogen, carbon dioxide, and organic acids, which may not be cleared as readily from the intestinal lumen.

The acidification of intraluminal contents for a prolonged period of time causes a reduction of local pH, which may result in injury to the intestinal mucosal, dissociation of divalent cations resulting in increased ionized fractions, and change in the spatial configuration of intraluminal proteins. These changes in protein spatial configuration may be able to trigger a release of vasoactive substances that then alter intestinal microcirculation[54,55].

Bifidobacteria release less endotoxin than Gram-negative bacteria; they therefore induce the release of reduced amounts of inflammatory mediators such as interleukin-1, interleukin-6, and TNF[56].

3. IMMATURITY OF THE GASTROINTESTINAL MUCOSAL BARRIER

The immaturity of the gastro-intestinal mucosal barrier can be demonstrated by:
1) Increased permeability of intestinal mucosal to intact proteins[57-61];
2) Reduced gastric acid secretion during the first week of life[62];
3) Reduced concentration of proteolytic pancreatic enzymes[63,64], enterokinase[6], and disaccharidase and lactase[66];
4) Immaturity of gastrointestinal motor activity[66,67];
5) A molar ratio of carbohydrate-to-protein that is less in the newborn mucus (The total protein content in intestinal mucus from newborn rat is greater than in adult mucus.[68]);
6) Structural modifications of intestinal microvilli; and [69]
7) Cellular and humoral gastro-intestinal immaturity[70,71].

4. PRENATAL CORTICOSTEROIDS AND NECROTIZING ENTEROCOLITIS

Several studies[72-81] have analyzed the maturation of intestinal mucosa following the administration of thyroid hormones[72-74] and steroids[75-81].

Israel et al.[81] have demonstrated in an animal model that prenatal administration of corticosteroids reduces the uptake of macromolecules from the intestinal mucosal[82], decreases small intestinal bacterial colonization with aerobic bacteria, and reduces the incidence of bacterial translocation to the liver, resulting in a lower incidence of NEC. The association between prenatal administration of corticosteroids and decreased incidence of NEC has also been demonstrated in neonates[79,83].

The effect of administration of corticosteroids on different enzymes has also been demonstrated[77,78,80]. Buchmiller et al.[80] have shown an enlargement of the small intestine and a trend of increasing lactase and maltase activity after administration of corticosteroids. Engelhardt et al.[77] have demonstrated that the prenatal administration of dexamethasone stimulates maltase and sucrase activities; however, no effect was observed on catalase, superoxide dismutase, and xanthine oxidase activities. Horváth et al.[78] have shown that the prenatal administration of betamethasone stimulates Na/K – ATPase enzyme activity.

FINAL CONSIDERATIONS

The findings described above suggest that the administration of prenatal corticosteroids is associated with maturation of intestinal mucosal; however, further studies are necessary to better understand the mechanisms by which corticosteroids exert their effects.

RESUMO RHCFAP/3100

PRECIOSO AR e col. – Enterocolite necrosante: resposta imflamatória x corticoterapia pré-natal. **Rev. Hosp. Clín. Fac. Med. S. Paulo 57**(5): 243-248, 2002.

A enterocolite necrosante é a mais freqüente patologia gastrointestinal adquirida no período neonatal, acometendo preferencialmente o recém-nascido prematuro.

Estudos experimentais sugerem que a corticoterapia pré-natal acelera a maturação da mucosa gastrintestinal, levando a diminuição da incidência desta doença.

Os autores apresentam uma revisão da literatura em relação aos principais fatores fisiopatológicos associados a enterocolite necrosante, tais como mediadores inflamatórios gastrintestinais, nutrição enteral e colonização bacteriana e imaturidade gastrintestinal e enfatizam a necessidade de mais estudos que avaliem a influencia da corticoterapia pré-natal com fator de prevenção da enterocolite necrosante.

DESCRITORES: **Enterocolite necrosante. Recém-nascido. Prematuridade. Corticoterapia. Fisiopatologia.**

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