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Protective Impact of L-arginine against Necrotizing Enterocolitis: A brief review

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Abstract

Necrotizing enterocolitis (NEC) is the most common acute surgical disease in preterm infants in intensive neonatal care unit. Premature infant is the infant born prematurely and have a low birth weight. The disease is characterized by an inflammatory process in the intestines, which sometimes worsen and reach the level of necrosis and, later may result in intestinal perforation and peritonitis, endangering the child's life. Different studies showed that arginine level in many premature infants is low, and subsequent studies have linked low arginine plasma concentrations with NEC disease. This paper concerned with raising awareness of this disease, its symptoms and its causes, in addition to pointing to the role of L-arginine; a semi-essential amino acid as an effective medication for necrotizing enterocolitis (NEC).

1. Introduction

Necrotizing enterocolitis (NEC) is a complicated disease represents bacterial invasion, necrosis of intestinal tissue, and inflammation. NEC is a destructive gastrointestinal disease and a most serious clinical problem which affects preterm infants. This problem has also been one of the biggest troublesome diseases in the neonatal care centers (Heida, 2016).

NEC disease was broadly recognized after the growth of modern neonatal intensive care units. The occurrence of NEC rose during the 1970s, because of the raise of neonatal survival percentage produced from seminal development in neonatal attention and care, like Continuous Positive Airway Pressure. The amendments in neonatal care and comprehensive studies and researches related to NEC is increased and developed, but the annoying truth is that the survival of neonatal with NEC in the past quarter of the century has not changed (Heida, 2016).

There are different expected factors exaggerating the NEC arise, and have been involved in the NEC pathogenesis. These expected factors are associated with unorganized patterns of gut bacterial colonization by bacteria, intestinal ischemia, and loss of intestinal epithelial barrier integrity, immune system immaturity, host mucosa defense mechanisms, and formula feeding (Henry and Moss, 2008).

The diversity mechanisms of NEC make it not fully understood which limit the NEC treatment, and makes it more challenging. Discontinuation of the oral feeding and providing of IV fluids and antibiotics can help in managing NEC treatment in its early periods. But, in advanced cases surgical intervention may be required, like abdominal drainage. These complex operations constitute a high risk in these periods (Henry and Moss, 2008).

Quick diagnosis and medical intervention can assist in saving the patient, but early diagnosis alone cannot always alter the patient's outcome, due to the rapid spreading of the disease, even before the coming of clear symptoms (Hunter, 2008).

Etiology of necrotizing enterocolitis (NEC) is still vague. So, NEC care, treatment, and prevention strategies are often unsuitable. Accordingly, understanding the causes of NEC are important, to detect the secrets of the appropriate therapy method.

Sometimes, and in countable hours, NEC spreads and transforms from early symptoms of intestinal inflammation to extensive necrosis, which make therapy and secondary prevention hard to attain. So, primary prevention must have the preference (Chen et al, 2014). Therefore, this paper is concerned with awareness of this disease, its symptoms and its causes, in addition to pointing to L-arginine (a semi essential cationic amino acid) medication role in necrotizing enterocolitis treatment (Shah, 2004).

2. Necrotizing Enterocolitis (NC): Pathology, Sign and symptoms

Necrotizing enterocolitis (NEC) is a medical case where a part of the intestine underwent necrosis and complete damage. This process can destroy intestinal wall and, later, cause a perforation. Intestinal contents, in

this case, leak to the abdominal cavity, endangering the child's life (Rich, 2017). Symptoms may include bloating, poor feeding, blood in the stool, or vomiting (Rich, 2017).

Figure (1): Normal Intestine Section versus Necrotic Section (Shelley, 2017)

NEC is reported as the most popular and serious life-threatening surgical and medical emergency of the intestine faced in preterm infants. It was first known and described in 1965 (Mizrahi et al, 1965 and Kliegman 1993), but it was not widely recognized until after developing of neonatal intense care (Obladen, 2009). NEC is influencing 5% - 10% of preterm infants, who are less than 36 weeks of pregnancy and less than 1500 g, with a related death rate of 10% - 50% (Chu et al., 2013).

Important morbidity is faced by surviving patients with NEC, like problems of feeding, neurodevelopmental impairment, failure to thrive short, bowel syndrome, and reliance on parental nutrition (Horbar, 2002). In which, it may lead to increase the intravenous duration of nutrition in infants, and then increase the danger of intended complications and the duration of hospitalization (Stoll et al, 2002).

There are different complex and multifactorial causes affecting NEC development, and are shown in Table [1] below**.**

Table [1]: Risk Factors for Necrotizing Enterocolitis, From Roberton's Textbook of Neonatology (Fox TP et al, 2012)

Prematurity
Intrauterine growth restriction
Placental abruption
Premature rupture of membranes
Perinatal asphyxia
Low Apgar score
Umbilical catheterization
Hypoxia and shock
Patent ductus arteriosus
Hypertonic feeds
Nonhuman milk formula
Rapid introduction of enteral feeds
Fluid overload
Pathogenic bacteria
Thrombocytosis
Anaemia
Polycythaemia
Exchange transfusion
Cyanotic congenital heart disease

3. Pathology

NEC diagnosis is depending on radiologic and clinical results. Pathologic examination of resecting entrails parts and autopsy specimens has been the foundation for improvement of pathogenesis theories.

NEC pathology is related to intestinal infarction variations from intestinal infarction. The cecum, right colon, and terminal ileum are reported as major parts to be affected in NEC, but entire colon and small intestine may be influenced in serious situations. Necrotizing Enterocolitis overall occurrence is, frequently, segmental necrosis with skip regions, but there is a persistent segment with circumferential necrosis. The influenced regions are distended with tenderize walls which may be dark red to black as shown in Figure [2].

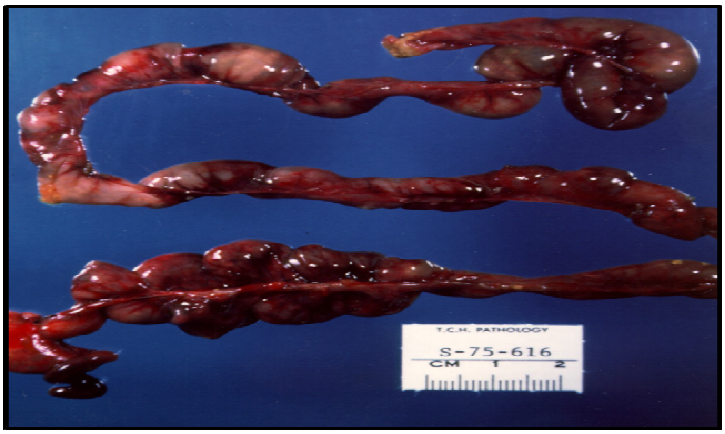

Figure [2]: Neonatal NEC with multifocal swelling and foci of nearly transmural necrosis (Hansen K, 2000)

In the case of perforation, gray-green exudate appears on the peritoneal fluid. Perforation is present in approximately 50% of patients (Balance et al, 1990 and Joshi, 1994). The appearance of pneumatosis intestinalis, if present, is as subserosal gas bubbles as shown in figure [3]

Figure [3]: Pneumatosis Intestinalis in NEC (Hansen K, 2000)

Sever stage of necrotizing enterocolitis is a mix of inflammation and coagulative-type necrosis. The characteristic feature in NEC are intramural vascular thrombi accompany the necrosis, mucosal edema, hemorrhage, and transmural bland necrosis related to perforation. Intestine which has suffered from NEC and is not amputated at the acute stage of the disease may expand to peripheral submucosal fibrosis at the healing phase. This procedure manifests clinically as strictures, and was found in 10-20% of infants of 3-10 or more weeks after the NEC diagnosis (Kosloske, 1980).

4. Sign and Symptoms

In premature infants, the beginning of NEC is often at the first weeks of birth. The recorded onset

average age is 1-3 days, but it may happen as late as age 1 month. The pathogenesis of the NEC disease, is not completely understood, is supposed to be multifactorial 14-16. These factors attached to inflammation and intestinal ischemia, aberrant bacterial colonization, and enteral feeding, and they have a big role in the NEC development in premature infants (Thompson & Bizzarro, 2008).

The knowledge of NEC disease until now is based on results generated by examiners seeking to preferable grasp of the clinical epidemiology of the patient-specific risk factors related to NEC, and the impregnable features of it as understood in the situation of the premature gastrointestinal (GI) system (Lin, P. W., Nasr, T. R., & Stoll, 2008)

There are different Initial symptoms that may be invisible and can include one or more of the following symptoms: diarrhea, delayed gastric emptying, hematochezia, ileus/decreased bowel sounds, vomiting, abdominal distention, abdominal tenderness, or both, and abdominal wall erythema (advanced stages) (Shelley, 2017).

In severe stages, there is a recurrent appearance of damage to one or more organs produced in pulmonary, renal and/or hepatic failure (Mitidiero LF et al, 2014). It develops into advanced systemic shock with hypotension, metabolic acidosis, oliguria, and disseminated intravascular coagulation (DIC) (Lin et al., 2005).

In full-term infants, NEC is often linked with implicit disorders, like congenital anomalies (myelomeningocele, perinatal asphyxia, and congenital heart disease), polycythaemia, respiratory distress, cows' milk protein-induced enterocolitis and glucose-6-phosphate dehydrogenase deficiency, and these disorders have been discussed as possible pathophysiological techniques (Lin & Stoll, 2006).

5. L- Arginine and Necrotizing Enterocolitis Studies

Different studies showed that the arginine level in many premature infants is low, and subsequent studies have linked low arginine plasma concentrations with NEC disease (Douglas, 2004).

Deficiency of Arginine - which is the basic content in the production of Nitric Oxide (NO) - may lead to vasoconstriction and gut injury, leading in the end to NEC. So, Arginine has the ability and a big role in decreasing the NEC development in premature infants (Akisu, 2002).

NO is very essential in normal gastrointestinal function due to different reasons. First reason is that Nitric Oxide is a substantial organizer of vasomotor function. Low NO concentration will lead to vasoconstriction of the gastrointestinal vessels, and then increase the NEC possibility. Second reason is that NO works as a neurotransmitter for enteric non-adrenergic non-cholinergic neurons. So, the lack of NO has the ability to change intestinal motility. Third reason is that NO prevent leucocyte adherence and modify the inflammatory restraints in the intestine (Akisu, 2002). Thus, L-arginine is essential to attain ordinary NO concentration in the GI tract.

NO has a volatile nature, so it cannot be used in GI tract in its present type. Then, supplementing substrates such as arginine must be used for its production and achieving sufficient concentration of it.

NEC is associated with metabolic function abnormality (Richir et al., 2007), and then reduces the concentration of plasma arginine (Zamora et al., 1997 and Becker et al., 2000).

Most of arginine supplementation information proposed a useful effect against NEC in premature infants, but is important to warn that arginine supplementation is warranted, because misadventures with different factors and treatments have a strong precedent in neonatology (Robertson and Baker, 2005). Caution proposed by Canadian Society of Critical Care about this case is found in studies conducted in adults, and resulted the increased death-rate in patients with pre-existing sepsis who were had arginine supplements (Heyland et al., 2003).

In contrast, different studies involving that NO has a harmful effect as an inflammatory mediator, and these studies cannot be ignored. Ford (2006) has stated that NO may has a role in the epithelial destruction pathogenesis in NEC, by the producing of peroxynitrite. This process will cause an enterocyte apoptosis and an inhibition of enterocyte proliferation and migration, and then leading to a gut injury cycle and uncontrolled inflammatory response. This will also affect further tissue destruction, intestinal perforation and systemic sepsis.

Researchers, in fact, found that there is a relationship between low concentrations of both asymmetric dimethylarginine (ADMA) and arginine in the plasma of premature infants with NEC. They proposed that the low concentrations of arginine are related to a low capacity in producing NO, due to low substrate for the reaction of nitric oxide synthase (NOS). This would prevent vasoconstriction and gut injury (Amin et al., 2002).

ADMA is a powerful endogenous competitive inhibitor of NOS. L-arginine and ADMA are in a

competence for the active site of NOS and for transport-mediated uptake into cells (Leiper & Vallance, 2006).

6. Conclusion

Arginine encourages the excretion of different hormones and is a metabolic foreboding of creatinine and creatine. In the neonate, the main metabolism of arginine also varies from that of the more mature infant.

L-arginine has an important protective impact against NEC disease. In fact, L-arginine may not avoid NEC injury completely; however the use of it at the first days of preterm infant's life could lead to NEC progression delay and raise the severity of this deadly disease.

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