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Effects of Breast Milk on Necrotizing Enterocolitis

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Abstract

Necrotizing enterocolitis (NEC) is one of the deadliest diseases a newborn could contract while in the neonatal intensive care unit (NICU). NEC is an inflammatory intestinal disease that is characterized by variable intestinal injury, inflammation and often bacterial invasion (Alganabi, Lee, Bindi, Li, & Pierro, 2019). This disease affects almost 10% of preterm infants weighing less than 1500 grams at birth and the mortality rate for infants weighing less than 1000 grams at birth is 30-50%. The pathophysiology of NEC includes a variety of factors and is still not completely understood. This literature review was written to examine the effects of breast milk on necrotizing enterocolitis. The literature review contains articles retrieved from online databases including CINAHL, and PubMed. The literature is still very new on the subject, and research is still being conducted, however, breast milk appears to play a very important role in the development of the infant's intestinal tract.

Keywords: Benefits, breast milk, human milk, necrotizing enterocolitis, preterm infants

Effects of Breast Milk on Necrotizing Enterocolitis

Early recognition and aggressive treatment have been key factors when improving the outcomes of infants with necrotizing enterocolitis (NEC) however, this disease still affects infants across the world. One of the reasons there is a high incidence rate in various hospitals is the difficulty in defining the condition. In 1978 Dr. Martin Bell developed the first clinical guidelines for diagnosing NEC called Bell's Classification or Bell's Criteria (Gregory, DeForge, Natale, Phillips & Van Marter, 2011). In the many years since then it has been modified as technology and medicine have advanced. Bell's staging criteria use systemic signs, findings in the abdominal examination and radiographic clues to stratify NEC in three different stages of increasing severity (Gupta & Paria, 2016). Stage I includes many common clinical conditions like feed intolerance, non-gut related sepsis and the abdominal features appear very non-specific. According to Gupta and Paria (2016) in the early stages of NEC, the abdominal features are non-specific and can manifest as increased prefeed gastric residual volume (GRV), vomiting, mild to moderate abdominal distension and bloody stools. These symptoms are rather vague and can point to a wide variety of other conditions. Additionally, more definitive signs such as tenderness and guarding appear very late, furthering the difficulty of early diagnosis and intervention. There is also debate between professionals as to what intervention should look like for these infants. The goal of this literature review is to review an assortment of research-based articles to determine the effects that breast milk have on preventing and/or treating NEC.

Methods

Included in this literature review are peer reviewed journal articles selected from keyword searches in online databases including PubMed and CINAHL. Keywords used included: "necrotizing enterocolitis", "breast milk and necrotizing enterocolitis", "effects of

breast milk on necrotizing enterocolitis”, “human milk and necrotizing enterocolitis”, “donor human milk and necrotizing enterocolitis”, “mother’s own milk”, “necrotizing enterocolitis in preterm infants” and “necrotizing enterocolitis in low birth weight infants”. Articles that were selected were written in English and be published within the last five years.

Effects of Breast Milk on Necrotizing Enterocolitis

All studies included in this literature review have shown that human milk serves a wide variety of functions for infants including protection against infection, enhancement of gastrointestinal maturation and dietary nourishment. In addition, the components of breast milk change to meet the infant’s needs as they grow and it is also believed to help development of the gastrointestinal system through immunomodulatory as well as antimicrobial actions (Burge, Hannah, Eckert, Gunasekaran & Chaaban, 2019). There is a group of compounds found in human milk and on the cell surface of the intestine called glycosaminoglycans (GAGs). One of the most prominent GAGs in human milk is chondroitin sulfate which comprises about 55% of the total GAG content (Burge et al., 2019). Research on chondroitin sulfate has shown that the compound could have antibacterial, antiviral and anti-inflammatory properties. This study tested the influence of chondroitin sulfate on cell viability, bacterial invasion, bacterial translocation and the ability of chondroitin sulfate to aid in decreasing intestinal inflammation in the presence of bacteria. Results showed that even up to concentrations of 750 μ g/mL, cell viability was not altered. Additionally, the viability for all concentration test groups remained above 90% after 48 hours of exposure to chondroitin sulfate. There was a dose-dependent reduction in the percent invasion of bacteria, with the level of bacterial invasion at 750 μ g/mL of chondroitin sulfate being significantly lower than the control (Burge et al., 2019). At its highest concentration, chondroitin sulfate reduced bacterial invasion by 75%. When testing the protection against

bacterial translocation, researchers found that by the third hour of exposure, the 750 μ g/mL solution reduced translocation by about 75%. Overall, this study shows that chondroitin sulfate, one of the most prominent GAGs in human milk, has the ability to protect against intestinal infection in an in vitro system, while creating no decrease in cell viability.

The risk of developing NEC at any gestational age may be related to the choice of milk used, the quantity and the timing of milk introduction (Herrmann & Carroll, 2014). Those three factors combined are known as feeding practice. This observational single-site study chose a cut off of 33 weeks gestational age and postmenstrual age (PMA) in which any period younger than this, and exclusively human milk diet was recommended. Their hypothesis was that for any infant younger than 33 weeks PMA would receive and exclusively human milk diet and reduce the incidence of NEC related to enteral feeding. During the study period all of the mothers with infants in the NICU were encouraged to express their breastmilk with hospital-grade breast pumps, but when mother's own milk (MOM) was not enough to meet the infant's needs, pasteurized donor human milk (DHM) was obtained from a human milk bank. In order to prevent any exposure to bovine proteins prior to 33 weeks PMA, human milk was fortified with a commercial human milk-based product (Herrmann & Carroll, 2014). Infants were receiving parenteral nutrition until enteral feedings could reach up to 140mL/kg/day. For this study they defined NEC as stage 2 or higher using Bell's classification. The EHM cohort included 162 infants and of those 148 (91%) received an EHM diet through 33 weeks PMA. There were 17 cases of NEC in the 443 (3.8%) infants in the control cohort and in seven of 199 (3.5%) in the EHM cohort. There was a significant reduction of NEC in the EHM cohort for the day of onset and the PMA at onset. Many NEC occurrences in the EHM cohort presented on day six or seven, before much enteral milk could be provided. The onset of NEC after day seven, during the

enteral nutrition phase, was rare for the EHM cohort at only 1% (Herrmann & Carroll, 2014).

This study shows that infants receiving an EHM diet have decreased occurrences of NEC during the enteral nutrition phase.

Mothers who deliver very low birth weight (VLBW) infants are not as likely to express their own milk. When challenges are faced regarding obtaining mother's own milk, the next best substitute would be donor human milk (DHM). The goal of this study was to examine whether DHM availability affects breastfeeding rates among VLBW infants and rates of NEC (Kantorowska et al., 2016). The data for this study was obtained through the California Perinatal Quality Care Collaborative (CPQCC) which gathers information on the care of >90% of California's NICU admissions and VLBW infants as well as the Mothers' Milk Bank of San Jose (MMB) which is the largest human milk bank in the United States (Kantorowska et al., 2016). Results showed that during the study period of 2007-2013, the number of NICU's receiving DHM increased from 55 to 133. There was a transition of 22 hospitals that went from having no DHM to have DHM during the study. These included a variety of care levels being provided and a total of 10,823 infants being cared for. The mean difference at each hospital was a 10% increase in breastfeeding at discharge, correlating the introduction of the DHM and the rate of breastfeeding upon discharge. Among the 22 hospitals that went from no DHM to having DHM available, the average decrease in NEC was 2.6%. The researchers combined the rates of breastfeeding at all the hospitals and the combined rate of breastfeeding at discharge increased from 52.8% to 61.7% after DHM was introduced. They did the same for the rates of NEC after DHM became available and it decreased from 6.6% to 4.3%. This study shows that the availability of DHM is linked to improved rates of breastfeeding and decreased rates of NEC.

Like the previous study, these researchers wanted to look at the rates of NEC related to DHM, but they completed a single center, observational and retrospective cohort study in the NICU where they worked. One cohort (Group 1) of 99 infants used premature artificial formula and the other (including 128 infants) used donor milk (Group 2) if mother's own milk was unavailable. Inclusion criteria were infants born at or before 32 completed weeks of gestational age, admission before 24 hours of life and survival longer than a week. Exclusion criteria were the presence of major congenital malformations, chromosomal, genetic or metabolic abnormalities or the absence of clinical records. Group 1 was studied in a two-year time period before the hospital received DHM and Group 2 was studied in a two-year period after the hospital received access to DHM. They found that the percentage of children receiving MOM was the same in both groups and there was a rate of 56.8% for exclusive breastfeeding at discharge. The incidence of NEC was slightly lower in Group 2 (9.1% vs. 3.4%), especially in the group with a gestational age between 28 and 32 weeks at birth (Vazquez et al., 2019). It was also determined that a history of NEC was more frequent among very preterm infants that eventually died in Group 1. On their unit, since the introduction of the DHM there has been a decrease in NEC rates, especially in the group of 28-32 weeks at birth. This study supports the evidence that DHM is a safe and beneficial option for very preterm infants without impairing their nutrition.

A factor to consider when deciding whether to use human milk or formula while in the hospital is the cost. A NIH-funded prospective observational cohort study completed by Johnson, Patel, Bigger, Engstrom and Meier (2015) examined the incidence of NEC, NICU hospitalization cost and cost of individual resources used during NICU hospitalization. In this study they wanted to look at using the cost of NEC as a strategy for the exposure period of human milk feedings

given to VLBW infants during NICU stays. The study took place at Rush University Medical Center from February 2008-June 2012. They took both direct and indirect costs for the NICU hospitalization from RUMC's system-wide cost account system and adjusted them to 2012 USD. The dose of human milk was calculated as both a weight-adjusted dose (ml/kg/day) and percentage of enteral feedings equal to human milk (Johnson et al., 2015). It was determined that the mean total NICU stay cost was 180,163 USD \pm 100,824 for infants with NEC and 134,494 USD \pm 72,604 for infants without NEC. During the study, 29 of the 291 infants developed NEC. The infants that developed NEC had longer hospitalizations and higher costs per day. The infants who had NEC requiring surgery accrued costs more than twice that of medically managed NEC. After controlling for other variables, NEC was associated with 43,818 USD in additional costs for the NICU hospitalization (Johnson et al., 2015). After controlling for NEC, each additional ml/kg/day of human milk in days 1-14 was associated with a reduction of 534 USD in non-NEC-related NICU costs (Johnson et al., 2015). They also discovered that infants with any exposure to formula during days 1-14 increased their risk of NEC by three times. Researchers also mentioned that they did not control for other morbidities so it is possible that NEC costs may be even higher since infants who get NEC have an increased risk for other morbidities.

Strengths and Limitations

The strengths of this literature review include peer reviewed articles that discussed breast milk as a protective substance against NEC that were submitted within the last five years, indicating research is current.

Limitations of this literature review include limited access to articles with free access. There were many articles that could be accessed only through a subscription or payment. Additionally, many of the articles published on this topic were outside of the five-year inclusion

range. The articles included in this literature review mention the lack of research on this topic in recent years and how it lends to the lack of understanding of NEC and possible treatments.

Implications for Practice

The research compiled in this literature review include interventions that can be implemented without much difficulty. By providing mothers of NICU infants hospital grade breast pumps, lactation consultants, encouragement and support, many moms could be providing their baby with breast milk that has protective factors, anti-inflammatory factors and immune regulating factors. If the mother is unable to provide enough milk, then hospitals can investigate obtaining DHM from milk banks across the country. This can provide the baby with the nutrients and assistance that they need to help fight off infections while not negatively impacting breastfeeding upon discharge.

Implications for Research

NEC is such a multi-faceted condition that requires a lot more research. We are learning a great deal more about possible treatments, but it still needs to be determined what exactly is causing this deadly and expensive condition. A study looking at what elements of breastmilk provide the protection and fight off bacteria in an in vivo system would be very helpful in determining what we can provide the baby with in the hospital to help them prophylactically.

Discussion

Overall, breastmilk has been shown to have protective factors that help prevent infection in newborns and that change to meet the baby's needs as they grow older. Providing infants with formula may help them grow quicker because it contains specific calorie counts, but it does not include the factors developed specifically for that baby. In fact, it does not include any protective factors at all. Formula fed infants will receive the caloric intake necessary, but it could cost them

a healthy gastrointestinal system. Another factor that many people do not consider when thinking about formula versus breastmilk, is how it can affect the cost of the hospital stay. To begin with, the use of breastmilk cuts the cost of formula out of the equation. Also, with the evidence provided above, mother's own milk can help protect the baby against infection while formula does not. If the baby does not contract an infection during their hospitalization, their costs decrease dramatically. While there is still a great deal of research to be done on what exactly causes NEC and possible ways to treat it, breastmilk is an effective, easily attainable and safe option to help boost infants' immune systems and prevent infections.

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