Journal of Neonatal Nursing (2016) xxx, xxx–xxx

ELSEVIER

Jnn

www.elsevier.com/jneo

Original Article

Feeding intolerance, inflammation, and neurobehaviors in preterm infants

Tiffany A. Moore, PhD, RN, Assistant Professor[a,*,1], Rita H. Pickler, PhD, RN, FAAN, The FloAnn Sours Easton Professor of Child and Adolescent Health; Director, PhD & MS in Nursing Science Programs[b]

[a] *College of Nursing, University of Nebraska Medical Center (UNMC), Omaha, USA*
[b] *The Ohio State University College of Nursing, USA*

Available online ■ ■ ■

KEYWORDS
Feeding intolerance;
Preterm infants;
Allostatic load;
Brain–gut–immune axis

Abstract *Purpose:* Identifying relationships between feeding intolerance (FI), inflammation, and early measures of neurodevelopment may provide the basis for clinically relevant assessments for NICU clinicians and staff. The purpose of this secondary analysis was to examine the relationship of FI to inflammatory markers and/or neurobehaviors in the first week of life.
Methods: This was a retrospective, matched case-control design with data drawn from 114 infants born at ≤32 weeks gestation.
Results: Eight infants developed FI prior to full enteral feedings. These infants were more likely to have dysregulated levels of cytokines, specifically IL-6, and lower neurodevelopmental scores compared to infants without FI.
Conclusions: Results suggest physiologic dysregulation and an immature nervous system may contribute to the phenomenon of FI in preterm infants. Further research to identify the role of the brain–gut–immune axis on FI and other GI complications in this population is warranted.

Introduction

Feeding intolerance (FI), defined as a change in the feeding plan by decreasing or discontinuing feedings because of suspicion of enteral

* Corresponding author. 985330 Nebraska Medical Center, Omaha, NE 68198-5330, USA. Fax: +1 402 559 4303.
E-mail addresses: tamoore@unmc.edu (T.A. Moore), pickler.1@osu.edu (R.H. Pickler).
[1] Dr. Moore has participated sufficiently in the conception and design of this manuscript to take public responsibility for it.

http://dx.doi.org/10.1016/j.jnn.2016.09.009
1355-1841/

Please cite this article in press as: Moore, T.A., Pickler, R.H., Feeding intolerance, inflammation, and neurobehaviors in preterm infants, Journal of Neonatal Nursing (2016), http://dx.doi.org/10.1016/j.jnn.2016.09.009

intolerance (Moore and Wilson, 2011), is a potentially serious complication in the first weeks of life for preterm infants. FI can be associated with necrotizing enterocolitis (NEC), one of the leading causes of morbidity and mortality in this population (Patel et al., 2015). Thus, the occurrence of FI remains a concern for care providers in the neonatal intensive care unit (NICU).

Researchers have examined FI as a stress-related disease of the gastrointestinal (GI) tract using the theoretical model of *Allostatic Load and Complications of Prematurity* (Moore et al., 2014). This model posits that complications of prematurity, such as FI, are associated with physiologic dysregulation from chronic stress. The model was tested in a study in which it was found that infants with FI were more likely to have dysregulation of stress biomarkers (cortisol and oxidative stress) in the first weeks of life (Moore et al., 2013). Specifically, infants with FI had lower levels of urinary cortisol on day 1 and higher levels of salivary cortisol on day 14. Infants with FI also had extremely high levels of oxidative stress on day 7. Results supported the theoretical model and suggested that allostatic load may be related to the development of FI in preterm infants. Results also suggested a maternal influence on physiologic dysregulation during the neonatal period and in particular, the presence of maternal inflammatory biomarkers.

FI and inflammation are related by several mechanisms. For example, intestinal mucosal inflammation associated with microbial colonization is one mechanism described in the literature that may play a role in the development of FI. In a recent review (Di Mauro et al., 2013), the interactions between microbial colonization, brain–gut–immune axis, FI, and inflammation were discussed. As the neonatal microbiota is forming, the intestinal response to bacteria is to secrete pro-inflammatory cytokines such as IL-6 and IL-4 from T-helper type 2 cells. An adaptive immune system response is the release of T-helper type 1 cells to maintain immune homeostasis; commensal bacteria such as *Bifidobacteriacea* are believed to aid in this balanced immune response. The microbiota may also play a role in immunity and inflammation via the brain–gut–immune axis suggesting the nervous system plays a role in GI functions such as motility, secretions, and immunity. In preterm infants, the immature and underdeveloped GI tract and immature brain–gut–immune axis may exacerbate GI complications such as FI.

Another associated mechanism involving FI and inflammation is the stress response. Activation of the HPA-axis eventually leads to the release of cortisol whose mechanisms are believed to act as a GI protectant during periods of acute stress (Charmandari et al., 2005). Decreased levels of cortisol may lead to irritation and inflammation during acute periods of stress, which would lead to FI, consistent with Moore's findings reported above (Moore et al., 2013). This phenomenon has been recognized in the intensive care unit for the adult population (Marik, 2009). Critically ill adult patients show signs of FI (i.e. vomiting and lethargy) which is suspected to be the result of an underlying systemic inflammation. Specifically, the release of pro-inflammatory cytokines would suppress the HPA-axis resulting in dysregulation of cortisol. In preterm infants, similar changes in the autonomic nervous system related to allostatic load (AL) would then affect motility, inflammation, and secretions in the GI tract leading to FI (Mayer, 2000).

The occurrence of FI may adversely affect preterm infants in several realms. Although preterm infants with FI that does not progress to surgical NEC are believed to have better neurodevelopmental outcomes compared to infants with surgical NEC (Rees et al., 2007; Tobiansky et al., 1995; Wadhawan et al., 2014), little is known about the relationship between FI in preterm infants and neurodevelopment in the first week of life. However, the *Allostatic Load and Complications of Prematurity* model (Moore et al., 2014) posits that general stress of prematurity and exposure to stress in utero negatively affect outcomes in preterm infants, including FI and neurodevelopment. Identifying relationships between FI, inflammation, and early measures of neurodevelopment may provide the basis for novel and clinically relevant assessments for NICU clinicians and staff.

The purpose of this analysis was to examine the relationship of FI in preterm infants to inflammatory markers and/or neurobehaviors in the first week of life. The specific aims were to 1) determine correlations between FI and inflammation as measured by inflammatory cytokines obtained in the first week of life; 2) determine correlations between FI and neurodevelopment in the first week of life using scores on the Neurobehavioral Assessment of the Preterm Infant (NAPI) (Constantinou et al., 2005).

Methods

This secondary analysis used a retrospective, matched case-control design with data drawn from 114 infants born at $\leq$32 weeks gestation who participated in a larger study (Pickler et al., 2015).

Please cite this article in press as: Moore, T.A., Pickler, R.H., Feeding intolerance, inflammation, and neurobehaviors in preterm infants, Journal of Neonatal Nursing (2016), http://dx.doi.org/10.1016/j.jnn.2016.09.009