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ORIGINAL ARTICLE

Does mitigating pain decrease the risk of infection? The interactions between nociception and immune function

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Abstract Recent studies suggest that analgesic interventions may influence immune function and the development of infection in neonates. Although substantial literature exists for the bidirectional relationship between nociception and immune pathways, there is a paucity of rigorous research linking nociception and immune function with the incidence of infection. This article presents the best available evidence for the interactions between nociception, immune function and the development of infection. Rigorous research is urgently needed to determine if anesthetic and analgesic regimens can influence immunomodulation or boost immune function significantly to avert infection.

Introduction

Neonatal sepsis is an important global health challenge. Of the estimated 4 million neonatal deaths, 25% are attributed to the clinical syndrome neonatal

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sepsis (Qazi and Stoll, 2009). The significance of the high rates of infection and the occurrence of multi-drug resistant pathogens has increased the necessity to explore adjunct therapies to help decrease sepsis. Emerging research has focused on the interaction between the nociceptive pathway and immune function suggesting effective analgesic strategies may modulate immune function and decrease infection (Chiu et al., 2013). This critical review of the biomedical literature will explore the association between the nociception and immune function and the potential for that interaction to mitigate infection in critically ill neonates.

Background

Neonatal sepsis is a major cause of morbidity and mortality in neonates. Although morbidity of neonatal sepsis differs significantly from country to country, within the past decade, the incidence of early onset sepsis in developed countries varies from 1 to 5 cases per 1000 live births. In developing counties the incidence is higher, varying from 49 to 170 cases per 1000 live births (Li et al., 2013).

The development of neonatal sepsis is inversely proportional to gestational age and birth weight. In term neonates, the incidence of infection is around 0.1% compared to approximately 20% in preterm neonates. Decreasing birth weight correlates with an increased incidence risk of sepsis, 10% in infants with birth weights between 1000 and 1500 g, 35% in infants with birth weights of $<$1000 g and 50% in infants with birth weights of $<$750 g. While gestational age is a more precise determinant of immune function, the criterion is not as objective as birth weight. The two criteria are closely related, but influences such as intrauterine growth restriction may result in a small-for-gestational-age (SGA) very low birth weight (VLBW) infant. The SGA VLBW infant's immune potential and risk for infection may be more aligned with the infant's gestational age rather than the infant's birth weight. In infants of lower birth weight ($<$750 g) and gestational age ($<$28 weeks), risk of infection seems to be linked to immature host defenses, compared to more mature infants, where risk factors such as abdominal surgery, central venous catheter or endotracheal tube indicative of high-risk patients (Kaufman and Fairchild, 2004).

Technological advances in healthcare, including the extended use of invasive devices and the survival of immunocompromised infants have all contributed to the incidence of neonatal sepsis. One approach for preventing neonatal sepsis is to eliminate or reduce exposure to infectious agents in the neonatal intensive care unit. Environmental controls such as handwashing are effective as long as the application of the intervention is consistent (Collins, 2008). There have also been approaches to support the neonate's immune defenses. To this end, the results of pharmacological interventions have been discouraging. Clinical trials have not demonstrated a significant reduction in incidence of neonatal sepsis with hematopoietic growth factors granulocyte-macrophage colony stimulating factor and granulocyte colony stimulating factor (La Gamma and De Castro, 2002) or a decrease mortality caused by septic shock with the use of anti-endotoxin (Opal and Gluck, 2003) or anti-tumor necrosis factor and anti-interleukin-1 (Dinarello, 2001). The use of corticosteroids in sepsis have not been conclusive (Vincent, 2008), and continue to be investigated. Activated Protein C modulates coagulation and inflammation; however, due to significant bleeding risk it should no longer be used in any age category (Kylat and Ohlsson, 2012). The overall inability to enhance host defenses through these interventions highlights the need to explore adjunct therapies and conduct further research in this area.

Nociception is the ability of peripheral afferent neurons to sense noxious stimuli (Rittner et al., 2005). Nociception and immune function exhibit a bidirectional relationship, each function affecting the other as well as within system interactions. Although the association between the central nervous system (CNS) and immune function is well documented (Calvo et al., 2012; Grace et al., 2014; Ren and Dubner, 2010; Stein and Machelska, 2011), how that relationship affects the incidence of infection is all but absent from the literature. The purpose of this article is to present the best available evidence examining the relationships between nociception, immune function and infection, the role anesthesia and analgesia may play in decreasing infection.

Methods

Search strategy

Articles were identified from electronic databases PubMed January 1996 to February 2014, Medline January 1971 to February 2014, and CINAHL, January 1982 to February 2014. Medical Subject Headings (MeSH terms) were infant, neonate, newborn, sepsis, infection, immune system, nociception, and pain.