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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.

Selection criteria

Articles were included for review if they met eligibility criteria: (1) literature focused on the association between the immune function and nociception/pain, (2) prevention or mitigation of infection was one of the outcomes of the study, (3) article was published within the last 10 years. English language restrictions were imposed. Articles excluded from review were (1) journal articles without original data and (2) citations without full text (e.g. conference abstracts).

Results

Influence of immune function on nociception

In the classic description of inflammation, extracellular and interstitial compartment cytokines activate neuronal mechanisms to increase the sensitization of nociceptors (Ramesh et al., 2013). Initially cytokine produced by tissue macrophages cause dilation of small blood vessels and endothelial changes that allow extravasation of neutrophils and macrophages to migrate to the infected tissue. Proinflammatory cytokines interleukin-1beta (IL-1β) and tumor necrosis factor alpha (TNF-α) are the first to be released, followed by interleukin-6 (IL-6) which lead to further migration through the vascular endothelium and accumulate at the site of inflammation (Janeway et al., 2005). Neurogenic inflammation signals the primary afferent neurons to generate impulses activating adjacent nerve terminals. The adjacent nerve terminals release pro-algesic nerve growth factor and prostaglandins that cause pain in the inflamed area (Ren and Dubner, 2010). Cytokines and chemokines released in proximity to nerve endings contribute to the activation of nociceptors and the development of hyperalgesia (DeVon et al., 2014).

Interestingly, migrating immune cells also have analgesic effects mediated by opioids in the periphery and CNS. The immune cells that infiltrate the inflamed tissue produce and contain endogenous ligands for peripheral opioid receptors (Stein and Machelska, 2011). Released concurrently with proinflammatory cytokines, the analgesic mediators β-endorphins, met-enkephalin, dynorphin, endomorphins provide peripheral endogenous opioid analgesia (Rittner et al., 2008). Anti-inflammatory cytokines IL-4, IL-10, and Il-13, released later, also contribute to peripheral endogenous opioid analgesia (Rittner et al., 2005).

Influence of nociception on the immune function

Neonates are capable of mounting an endocrine and metabolic response to pain and stress (Anand et al., 1985). The dense network of afferent nociceptive fibers that innervate the neonate's skin, gastrointestinal tract and respiratory tract are frequently exposed to bacterial pathogens. Stimulated by the bacterial infection, immune cell recruitment results in inflammation and pain (Ren and Dubner, 2010). Pain and stress activate the hypothalamic-pituitary-adrenal axis (HPA) decreasing insulin and increasing growth hormone and cortisol resulting in hyperglycemia.

Among neonates exposed to pain and stress the most consistent metabolic effect is hyperglycemia (Anand et al., 1987). Hyperglycemia adversely impairs phagocytosis of bacteria, promotes the exponential bacterial growth and increases the virulence of bacteria (Philips et al., 2005). Studies demonstrate that acute, short-term, in-hospital hyperglycemia and even relatively mild, preexisting hyperglycemia affect all major components of immunity and impair the infant's ability to combat infection (Derr et al., 2008; Matias Cdo et al., 2013). Turina et al. (2005) found control of hyperglycemia is associated with a decrease in infection.

In a study that has the potential to change the way health care professionals think about painful infections, Chiu et al. (2013) challenge the established relationship between pain and inflammation. The assumption is that the relationship between pain and inflammation is indirect, that immune cells are activated and release factors that act on nociceptive neurons that cause them to respond more sensitively. What the scientist discovered was that during an infection, almost immediately, bacteria make molecules that acted on nociceptive fibers causing them to generate pain signals. The reported pain levels correlated closely with bacteria load and peak well before tissue swelling keeping with the hypothesis that the bacteria are the source of the pain and not the local inflammatory response. Once activated by the bacteria, the pain neurons suppress immune function. In other words, the nerves "know" the bacteria are there before the immune system becomes active. The nerves launch the pain signals that decrease immunity.

Chiu et al. (2013) hypothesize that the nociceptive neurons are protecting the infected tissue from further damage caused by the inflammatory immune response. It is a protective mechanism the

bacteria exploit. Chiu et al. believe if pain can be blocked in infected tissues and analgesic interventions can block the interaction between pain neurons and the immune system, then the treatment of bacterial infections can be improved. This novel approach proposes that blocking pain can increase an individual's immune response and mitigate bacteria's strategic advantage.

Effect of anesthesia and analgesia on the development of infection

Metabolic, endocrine, immune function and neurological activity are altered by pain and stress in neonates. These responses are affected by anesthetics and analgesics. The interactions between nociception and immune functions suggest that anesthesia and analgesic interventions may modulate immune function and may have the potential to reduce the incidence of neonatal sepsis in critically ill neonates.

Influence of anesthesia on immune function

The mechanisms by which anesthetic agents reduce or prevent the stress originating from painful procedures is well described, yet little in know about how anesthetics affect immune function. In a study comparing deep anesthesia (sufentanil) to a lighter anesthesia (Halothane) Anand and Hickey (1992) found newborns who received sufentanil had a decreased incidence of sepsis, disseminated intravascular coagulation, metabolic acidosis and death. These neonates also had significantly reduced responses of epinephrine, norepinephrine, β-endorphin aldosterone, glucagon and cortisol and other steroid hormones. The neonates receiving sufentanil also had better responses to insulin with less hyperglycemia. The study shows physiologic responses to stress are attenuated by deep anesthesia.

Studies exploring the effects of anesthesia on immune function and infection in neonates have been absent from the literature for several years, however preclinical trials and adult data show promise for reduction of stress response. Fuentes et al. (2006) demonstrated that a one hour continuous administration of anesthesia after a toxic dose (20 mg/kg of body weight) of *Escherichia coli* lipopolysaccharide (LPS) resulted in a significant increase in survival compared with survival of non-anesthetized mice. Anesthesia protection correlated with a delay in plasma *E. coli* LPS circulation and a delay in inflammatory response, particularly serum levels of tumor necrosis factor alpha (TNF-α), results suggest that anesthesia has an important impact on the outcome from endotoxemia.interleukin-6 (IL-6), and IL-10. Different classes of anesthetic agents produce the same effects on the inflammatory response. These results suggest that anesthesia has an important impact on the outcome from endotoxemia.

A multimodal approach to anesthesia appears to boost immune function. Cheng et al. (2013) examined two different anesthesia methods, general versus combined regional/general, in the treatment of benign ovarian tumor by laparoscopic therapy ($n = 160$). Percentages of T cells decreased significantly 2 h after anesthesia ($P < 0.05$) and again during surgery. However, T cell percentages in patients receiving combined anesthesia returned to normal levels 5 days after surgery, and those receiving only general anesthesia returned to normal by 7 days after surgery. In addition, the decrease in the combined group was less than the decline in the intravenous-only group ($P < 0.05$). These findings indicate that the effect of general anesthesia combined with thoracic epidural anesthesia on immune function was less than that produced by general anesthesia alone. Although these studies indicate that various anesthetic protocols affect immune function, their mechanism of action is still poorly understood.

Influence of analgesia on immune function

If pain is a factor in inflammation, then it seems logical to surmise that effective analgesic interventions could improve immune function. Indeed, in preclinical and clinical trials, many aspects of immune function have been compromised by nociception. Studies are producing evidence that demonstrate an interaction between analgesia and immune function and the development of infection.

Hong and Lim (2008) found preemptive epidural analgesia effective for controlling perioperative immune function and preventing postoperative pain in patients undergoing cancer surgery. In a randomized control trial, forty women undergoing elective laparoscopic radical hysterectomy for cervical cancer were allocated receive preemptive analgesia (2 mg morphine dissolved in 15 mL of 1% lidocaine) or normal saline prior to epidural analgesia. IL-6 levels in both groups increased after surgery but elevations were significantly less in the preemptive group compared to the control group. IL-2 levels in both groups were decreased after surgery, but 72 h later returned to baseline in the preemptive group but not in the control group. Pain scores at 6 and 12 h after surgery in the

preemptive group were significantly lower than in the control group.

Another study investigated the correlation between the administration of a specific analgesic (morphine) and the development of infection (Suzuki et al., 2013). Previous reports found morphine induced immunosuppression putting the patient at risk for infection. Development of infections was based on antibiotic administration and diagnosis of infections. In the retrospective study, the authors found patients treated with morphine were at greater risk for developing infections than those patients treated with other analgesics (odds ratio = 3.60, 95% confidence interval = 1.40—9.26). The findings suggested that some analgesics such as morphine's may have an immunosuppressive effect that contributes to the development of infections in patients.

Finally, anesthesia may reduce organ failure perpetuated by the inflammatory response in patients with sepsis. Lidocaine has been shown to locally modulate the inflammatory response and relieve pain. Berger et al. (2014) recently investigated the systemic effects of lidocaine on recruitment of leukocytes in adult patients with sepsis in a small randomized double-blind clinical trial ($n = 14$) including bolus of lidocaine 1.5 mg/kg versus saline followed by continuous weight based infusion over 48 h. Lidocaine reduced chemokine-induced neutrophils arrest and stopped transmigration of neutrophils which may reduce tissue injury associated with sepsis. Selectin mediating slow-rolling of neutrophils were preserved. Although these findings suggest a potential therapeutic role to decreased inappropriate leukocyte activation which may lead to overt cytokine release in sepsis (Kobayashi and Flavell, 2004), the authors did not describe measures of pain. They reported very high APACHE scores (over 30 in each group) and a majority in each group required vasopressors; therefore, there is a high likelihood that these patients were also receiving mechanical ventilation. Medications for pain and sedation are routinely administered in the setting of mechanical ventilation, and could have influenced their findings. These should be reported in future studies.

Little data is available on the effects of analgesia on neonatal infection but the emerging data favor a moderation of response. Study outcomes evaluating the effects of anesthesia and analgesia for decreasing the incidence of infection demonstrate positive outcomes at a cellular level and the reduction of proinflammatory cytokines. Whether these immune changes are able to decrease the risk and incidence of neonatal infection remains unknown.

Discussion

Strong evidence supports acute pain as a stressor that impairs immune function. Given the vital link between immune cells and the defense against bacterial and viral infections, it is incumbent upon nurses to preserve immune capacity to prevent neonatal infection. Encouragingly, there is direct evidence in preclinical trials and indirect evidence in humans that effective pain management via anesthesia and analgesia preserves immune function. Preclinical trials show appropriate pain management provides significant protection against infection. Although preclinical trials cannot be extrapolated to humans, emerging clinical evidence is aligned with the animal studies.

Maturation of immune response is not global, some processes mature earlier. Age dependant development of neurotransmitters, receptor expression, and synaptic transmission will affect immune response. Some functions such as neutrophil ingestion and destruction of pathogens are similar to adults while others such as chemotaxis are still immature in newborns (Carr, 2000). Maturation and developmental changes in the nervous system of infants provides vital insights into the interaction of nociception, immune function and infection. Pediatric and neonatal research is urgently needed to confirm if the interactions between nociception, immune function and infection in infants is similar to adults.

This review has several limitations. Levels of pain intensity and stress correlate with immune function (Padgett and Glaser, 2003). All but one study failed to report pain intensity or provide information on how pain was measured. The absence of a valid measure of pain is a significant threat to the validity of the findings. A second limitation is the lack of longitudinal data to determine if the incidence of infection is associated with the decrease in immune function. Future studies should consider anesthetic and analgesic regimens, monitor pain and immune responses, document endocrine and metabolic stress and follow up for the incidence of infection (Weatherstone et al., 2003).

While many observational and experimental studies convincingly demonstrate pain is responsible for significant immunosuppression and increases the rates of infection, the findings from

clinical studies are inconclusive. Strong evidence does not exist to support appropriate pain management as valid intervention for decreasing the incidence of neonatal infection. On the other hand, although no direct link has been confirmed with rigorous clinical trials, the data from the observational and experimental studies do not exclude the possibility that an analgesic regimen might provide a decrease in the incidence of neonatal infection.

Conclusion

This review highlights the many interacting relationships between the physiological systems that detect and respond to infection and those that respond to noxious stimuli. Although there is a paucity of evidence exploring these relationships, the high risk of acquiring neonatal infection and the significant adverse outcomes associated with infection are compelling reasons to explore analgesic and anesthetic approaches to support critically ill and immunocompromised neonates. Premature and critically ill infants are vulnerable to repeated painful procedures and the development of infection. Pharmacological interventions to boost immune functions have not met the standard for success. The robust interactions between immune function and nociception provide opportunities for provocative and innovative interventions supporting pain management as an adjunct therapy for mitigating neonatal infection. Preclinical trials and adult studies have provided intriguing data to guide future research, but more rigorous studies are required before it can be determined if anesthetic and analgesic regimens can influence immunomodulation or boost immune function significantly to avert infection.

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