Are There Opportunities to Decrease Nosocomial Infection by Choice of Analgesic Regimen?

Evidence for Immunity and Pain Interactions

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Background: Interactions suggest that anesthetic and analgesic strategies could be used to modulate immune function and reduce nosocomial infection in critically ill pediatric patients. However, this theory has yet to be adequately tested.

Objective: To present the evidence for interactions between nociceptive and immune pathways.

Data Sources: The MEDLINE database and hand searches of the English-language biomedical literature for the 1985-2003 period.

Data Synthesis: Substantial evidence exists for numerous bidirectional relationships between nociceptive and immune pathways. Some studies suggest that surgical pain and stress may alter immune function in adults. Limited evidence indicates that anesthetic and analgesic immunomodulation may boost immune function to prevent nosocomial infection. However, unique aspects of immune function maturation and neurodevelopment must be considered.

Conclusion: Research is urgently needed to determine if the interactions between nociceptive and immune function pathways in critically ill infants and children are similar to those in adults and if host defenses can be enhanced by optimal anesthetic and analgesic strategies.

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Nosocomial infection remains a significant complication in pediatric patients, particularly in the intensive care unit (ICU) setting. The combination of high rates of nosocomial infection and the emergence of multiresistant pathogens has increased the urgency to explore new approaches to this problem. Recent evidence indicates that pain and stress have complex effects on host immune and inflammatory responses and are likely to modulate host defense against infection. This critical review of the biomedical literature for the years 1985 to 2003 (retrieved from the MEDLINE database and hand searches) reveals important interactions between nociceptive and immune function pathways and suggests that anesthetic and analgesic strategies could be used to modulate immune function and perhaps reduce nosocomial infection in critically ill pediatric patients.

THE PROBLEM OF NOSOCOMIAL INFECTION

Recent studies indicate that the risk of late-onset sepsis and nosocomial infection remains a significant problem for neonatal and pediatric patients in the ICU setting. Despite improvements in bloodstream infection rates during a 10-year period, children in ICUs continue to exhibit the highest rate of these infections when compared with medical, coronary, and surgical ICU patients. The risk of nosocomial infection is reported at 6% to 7% for pediatric ICU patients and as high as 21% for neonatal ICU patients. Technological advances in patient care, including the widespread use of long-term invasive devices and the survival rates of patients who are immunocompromised as a result of disease, prematurity, or advanced therapies, contribute to the increasing incidence of nosocomial infection. One approach to prevent nosocomial infection is to eliminate or substantially reduce exposure to infectious agents in the hospital. Environmental changes, such as attention to proper hand washing and reduction of patient cross-contamination by staff, have proved effective as long as these measures are implemented with constant diligence. Other interventions, such as judicious antibiotic use, are important but have failed to halt the spread of antibiotic-resistant nosocomial infections in the tertiary care setting.
The second approach to the prevention of nosocomial infection is to supplement host defenses. The results of these interventions have also been disappointing. For example, intravenous immunoglobulin G prophylaxis in very low-birth-weight neonates was evaluated in several studies, including a large, multicenter randomized controlled trial. This trial showed no significant decrease in the incidence of nosocomial infections or improvement in other outcome measures. Administration of the hematopoietic growth factors granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor increased neutrophil counts and improved neutrophil function in animal and human infant studies. However, there is insufficient evidence that these changes decrease the incidence of infections in newborns. After multiple preclinical investigations and numerous clinical interventional trials, there is no evidence of a significant reduction in human mortality caused by septic shock with the use of antiendotoxin therapies in sepsis. One promising new approach is the administration of recombinant human-activated protein C, which has been shown to decrease mortality in adults with severe sepsis. It was recently approved in the United States and Europe for this use and is now being investigated in pediatric populations. Nevertheless, the overall lack of success of interventions to specifically boost host defenses highlights the need for further studies in this area.

**PAIN AND INFLAMMATION: A BIDIRECTIONAL RELATIONSHIP**

Critical illness, particularly sepsis, is a major risk factor for the development of infection because of profound effects on hormonal, metabolic, and host defense mechanisms. A large proportion of patients in ICUs are postsurgical, and surgery induces these same profound effects. Critical illness, particularly sepsis, is a major risk factor for the development of infection because of profound effects on hormonal, metabolic, and host defense mechanisms. After multiple preclinical investigations and numerous clinical interventional trials, there is no evidence of a significant reduction in human mortality caused by septic shock with the use of antiendotoxin therapies in sepsis. One promising new approach is the administration of recombinant human-activated protein C, which has been shown to decrease mortality in adults with severe sepsis. It was recently approved in the United States and Europe for this use and is now being investigated in pediatric populations. Nevertheless, the overall lack of success of interventions to specifically boost host defenses highlights the need for further studies in this area.

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response; and (3) surgical patients are at risk for nosocomial infection. Although the literature contains data on these subjects individually, there have been no studies to evaluate the linkage of these aspects of care in critically ill patients. This article discusses the available literature in the postoperative setting and points out areas in which future study may be fruitful.

EFFECTS OF INFLAMMATION ON NOCICEPTION

Cytokines are a large family of soluble, low-molecular-weight proteins that influence both immune and non-immune systems. They are produced by a variety of cells including monocytes, macrophages, glial cells, and endothelial and epithelial cells.16 Several different stimuli including trauma, infection, and reperfusion injury cause cytokine release, specifically increases in IL-6, TNF-α, and IL-1. These proinflammatory cytokines are key to the development of the immediate response to the insult, with further release of inflammatory mediators, changes in leukocyte traffic, and cardiovascular function. Cytokines also play a role in peripheral and central nociception, as shown by Watkins and Maier.17 For example, proinflammatory cytokines able to induce hyperalgesia at the site of an inflammatory insult18 have been shown to stimulate the formation of prostaglandins peripherally, resulting in sensitization of peripheral, or “silent,” nociceptors.17,19 In addition, prostaglandin E2 is released locally as a result of surgical tissue disruption and can suppress inflammatory host responses including natural killer (NK) cell cytotoxicity.20,21 Cytokines such as IL-1, IL-6, and TNF-α also modulate nociception via their effects on a range of molecules in the brain, in particular prostaglandins such as prostaglandin E2.22 Prostaglandins are a likely mechanism by which cytokines in the brain mediate pain responses. Brain-derived cytokines modulate additional functions controlled in the hypothalamus, such as thermoregulation, and can disturb sleep and feeding activities.22 These are symptoms commonly seen in patients with sepsis.

Other factors released during the inflammatory response to tissue trauma have nociceptive effects. These include bradykinin, which is a particularly strong stimulator of nociceptors, and serotonin.23 Nerve growth factor is released from peripheral fibroblasts, stimulating nociceptors with consequent hyperalgesia.24 In the presence of neurogenic inflammation, substance P is released.23,25 Substance P acts peripherally and centrally and induces degranulation of mast cells, which then release histamine.23 Histamine release causes vasodilation and plasma extravasation. As a result, the activation of cellular host defenses occurs with further release of algogens including bradykinin and serotonin.23 Immune cells (lymphocytes, monocytes, and macrophages) have antinociceptive effects mediated by opioids in the central nervous system and periphery. Endogenous ligands for peripheral opioid receptors are produced and contained in immune cells that infiltrate inflamed tissue.26,27 Endogenous opioids released with inflammatory pain include β-endorphin and met-enkephalin.28 Machelska et al29 demonstrated in a rat model that the process of leukocyte extravasation could result in peripheral endogenous opioid analgesia.

Interferon α (IFN-α), which is produced in the brain during viral infection and is critical for protection against these infections, may also bind to opioid receptors. In animal studies, intracerebral administration of IFN-α resulted in changes in central neuronal activity and signs of fever, anorexia, and analgesia.30 These effects were inhibited by naloxone, suggesting that binding of IFN-α to opioid receptors, which then inhibited N-methyl-D-aspartate (NMDA), mediated nociception.

Nitric oxide is an endogenous gas generated by specific nitric oxide synthases that exist in neuronal, endothelial, and macrophage cells. It is a vasodilator and is primarily used in clinical pediatrics to treat pulmonary hypertension.31 Both nociceptive and antinociceptive effects of nitric oxide have been described.32,33 The generation of central nervous system and peripheral site nitric oxide is caused by the release of substance P following afferent neuronal stimulation, followed by stimulation of the NMDA receptor by glutamate and leading to increased calcium, increased nitric oxide synthase, and the release of nitric oxide from the neuron. It has been shown that nitric oxide synthase is widely distributed in the brain34; nitric oxide diffuses out from the neuron and stimulates the formation of cyclic guanosine monophosphate. Nitric oxide can be excitatory or inhibitory depending on the expression of cyclic guanosine monophosphate–controlled ion channels in target neurons.35 A recent clinical study36 suggests that nitric oxide plays a role in analgesia. Patients with cancer who received nitroglycerine (a nitric oxide donor) along with oral morphine had decreased opioid use and delayed morphine tolerance.

EFFECTS OF NOCICEPTION ON INFLAMMATION

Afferent nociceptive input induced by surgical tissue trauma results in the experience of pain. Surgical tissue trauma, in the absence of operative anesthesia and postoperative analgesia, also activates hormonal and metabolic stress responses.36,37 The result of hypothalamic-pituitary-adrenal axis stimulation is an increase in cortisol and growth hormone and a decrease in insulin. The cortisol and endocrine changes cause hyperglycemia. Some evidence suggests that control of hyperglycemia, or perhaps the beneficial effects of insulin in response to hyperglycemia, is associated with improved outcomes in critically ill patients.37

Cortisol increases with surgical pain and stress and participates in pivotal interactions with host immune responses, both proinflammatory and anti-inflammatory.38 When this balance of effects is altered, cortisol inhibits host defenses, putting the host at risk for infection.39 In a study by DeAmici et al,39 vaginally delivered newborns had higher levels of cord blood cortisol and reduced NK cell activity compared with newborns delivered by cesarean birth with general anesthesia, who had only mildly elevated cortisol levels. This study showed that changes in a marker of stress and pain, cortisol, were associated with changes in host immune cells. Whether these immune cell changes identify patients more likely to develop nosocomial infection is unknown.

Sympathetic nervous system stimulation associated with surgical stress results in the release of catechol-
amines such as epinephrine and norepinephrine. These cause physiologic stress responses, including effects on heart rate and blood pressure. Catecholamines also result in increased blood glucose levels and a potentially increased risk of infection. Sympathetic nervous system input, particularly norepinephrine, is likely involved in the generation of nociception, hyperalgesia, and inflammation in the setting of tissue trauma.46

**EFFECTS OF ANESTHESIA ON IMMUNE FUNCTION**

The mechanisms by which anesthetic agents prevent or reduce pain-related stress responses in adults and children through central nervous system actions have been well described.31-41 Less is known about how anesthetics affect immune function. No studies examining the specific effects of various anesthetics on immune function have been carried out in pediatric patients. However, several recent adult studies demonstrate that various anesthetics have differential effects on immune function. In a randomized clinical trial, Crozier et al45 compared inhaled agents (isoflurane and nitrous oxide) with intravenous anesthesia (alfentanil and propofol) in patients undergoing elective hysterectomy. There was a greater increase in proinflammatory IL-6 and a more rapid increase in cortisol levels in the inhaled anesthesia group compared with the intravenous group. In another randomized controlled trial,46 patients undergoing hysterectomy received general anesthesia alone or with extradural anesthesia. Although there were no significant differences in perioperative IL-6 or C-reactive protein levels between groups, cortisol and growth hormone levels were attenuated in the group that received the extradural anesthesia. In a nonrandomized trial, Koltun et al47 compared immune function and stress responses in adult patients undergoing open colectomy with epidural anesthesia or conventional general anesthesia. Patients receiving general anesthesia showed a reduction in NK cell cytotoxicity from 36% to 22% compared with preoperative levels. No difference was seen in the epidural group. Trends showing decreased levels of plasma epinephrine and cortisol in the epidural group did not reach statistical significance. Urinary cortisol excretion during the first 24 hours postoperatively was significantly higher in the general anesthesia group compared with the epidural group, with no significant difference between groups preoperatively. Unfortunately, none of the trials reported patients’ pain intensity. Although these studies suggest that various anesthetic regimens affect immune function, the mechanisms (eg, central nervous system or peripheral immune cellular mediators) are not yet understood.

**EFFECTS OF ANALGESIA ON IMMUNE FUNCTION**

Postoperative analgesia reduces pain-related stress responses through peripheral and central nervous system actions that have been well described.38,43,48 Less is known about the effects of analgesics on immune function. Kim and Hahm49 randomized patients undergoing abdominal hysterectomy to either patient-controlled morphine or morphine plus ketorolac analgesia postoperatively. The pro-inflammatory IL-6 level increased immediately following the operation and remained elevated for 24 hours in both groups. However, the IL-6 level was lower at 24 hours in the morphine plus ketorolac group. The anti-inflammatory IL-10 levels peaked at 2 hours and then decreased, with the morphine plus ketorolac group having a higher IL-10 level at 4 hours. These findings suggest a less pronounced proinflammatory cytokine response (IL-6) and greater anti-inflammatory cytokine response (IL-10) in the group receiving the opioid plus ketorolac analgesia. Although there were no differences in visual analog pain scale or sedation scores between the 2 groups, there was a significant decrease in morphine use in the group receiving the opioid plus the anti-inflammatory agent. It is unknown how closely the anti-inflammatory and analgesic properties of these treatments are linked. This study shows that a specific strategy of postoperative analgesia clinically affected opioid use and lessened the postoperative pro-inflammatory cytokine response. Whether patients who received the combined therapy had fewer nosocomial infections is unknown; this is an area for future study.

Moon et al50 randomized adult patients with thoracic injury to epidural (bupivacaine plus morphine) vs parenteral (morphine) analgesia. The epidural group had decreased pain scores, a more rapid improvement in respiratory function, and decreased IL-8 levels compared with the parenteral analgesia group. There was a nonsignificant trend toward lower IL-6 levels in the epidural group and no significant differences in IL-1, IL-2, TNF-α, or urinary catecholamine levels. This study demonstrated a link between decreased pain scores, more rapid clinical improvement, and changes in an immune marker with one analgesic regimen compared with another. Whether changes in individual immune markers induced by opioid analgesia are associated with changes in response to infection or incidence of nosocomial infection remains unclear.

There is clearer evidence that nonsteroidal anti-inflammatory agents may directly affect immune function. For example, indomethacin sodium trihydrate increased NK cell activity, attenuated postoperative IL-6 release and bloodborne metastasis, and decreased pain in rats.51 Other studies suggest that these agents inhibit cyclooxygenase in the spinal cord and periphery, resulting in decreased prostaglandin levels and decreased hyperalgesia. They have also been shown to decrease cytokine expression during inflammation.18

In summary, there is evidence for modulation of the immune system by analgesia. These changes include effects on cellular activity (NK cytotoxicity) and the tendency for a reduction in proinflammatory cytokines with combined regimens and more targeted regional approaches. Whether these immune changes affect the risk of nosocomial infection is unknown, but this question presents opportunities for future study.

**NOCEPTION AND IMMUNE FUNCTION INTERACTIONS: CONSIDERATIONS FOR THE PEDIATRIC PATIENT**

Developmental changes in the nervous system may offer key insights into the interaction between nocicep-
tive and immune pathways. These changes in activity are due to the regulation of neurotransmitters and changes in receptor expression and function, changes in firing patterns of afferent fibers, and changes in synaptic transmission. Furthermore, developmental changes in afferent activity that occur during the postnatal period will inevitably affect the response to surgical tissue trauma. The reader is referred to several recent comprehensive reviews of sensory nervous system development.31-35 The process of immune response maturation in the newborn remains poorly understood. There is not a global immaturity, but rather some functions are comparable with those of adults, such as neutrophil ingestion and killing of pathogens, whereas others such as chemotaxis are reduced in the newborn.36 In studies of 26- to 42-week-gestation newborns, an increased proinflammatory IL-6 level was found postoperatively in both preterm and term infants.37 Interestingly, there was a linear correlation between IL-6 increase and operative stress score, indicating that the IL-6 level increased to a greater degree in relationship to the severity and extent of the procedure. It is unknown whether alterations in specific cytokine or other immune markers in response to analgesia are dependent on the stage of development, but this will be an important consideration in the evaluation of analgesic effects.

Peters et al38 showed that HLA-DR antigen was decreased in infants and children in pediatric ICUs and that the degree of suppression was related to the intensity of the illness. Patients with single system failure had less suppressed HLA-DR antigen compared with healthy children and adults, whereas patients with multiple organ system failure had a greater degree of suppression. Interestingly, HLA-DR antigen levels in patients who recovered from severe multiple system organ failure return to levels comparable with those of pediatric and adult controls. The authors postulated that patients with the greatest decrease in HLA-DR antigen would have the highest risk of nosocomial infection. This hypothesis was supported in another study39 in which children aged 36 weeks to 16 years undergoing elective cardiac surgery had decreased HLA-DR antigen from postoperative days 1 to 5 compared with preoperative levels. Importantly, in the first 72 hours, the HLA-DR antigen level was significantly lower in patients who subsequently developed sepsis or systemic inflammatory response syndrome (SIRS). These patients also had a significantly increased length of stay compared with patients who had less severe suppression of HLA-DR antigen. Furthermore, HLA-DR antigen was shown by Hallwirth et al40 to be a good indicator of culture-positive sepsis in very low-birth-weight neonates. The expression of HLA-DR antigen was significantly decreased in peripheral blood monocytes in neonates with sepsis compared with those without infection.

These studies are the first to show an immune marker that could be correlated with an increased risk of nosocomial infection in pediatric patients. They suggest that HLA-DR antigen may be a helpful marker for predicting patients with the highest risk of developing nosocomial infection. Whether the decreased level of HLA-DR antigen was related to surgical stress alone and whether the degree of pain was different in these groups are unknown because none of these studies measured pain or analgesia. However, the consistency with which monocye HLA-DR antigen level correlates with immune hyperresponsiveness indicates its potential usefulness in future studies of analgesia and immune function interactions. Only 1 study has reported the immune response to acute procedural pain in newborns. Rasmussen41 measured cytokines, cortisol levels, and changes in white blood cell panels in term newborns undergoing circumcision. Changes in neutrophil counts were correlated with intensity of pain as measured by the Premature Infant Pain Profile (PIPP).42 The higher the PIPP score, indicating more pain, the lower the neutrophil counts following circumcision.

The observations described previously indicate that immunological markers can be objectively measured in pediatric patients. On the basis of current evidence, these specific markers may be expected to change in response to pain or analgesia.

**SURGICAL PAIN AND STRESS**

Term and preterm newborns and infants are capable of activating endocrine and metabolic responses to surgical pain and stress.43-48 Metabolic work has been measured postoperatively via resting energy expenditure and respiratory quotient in newborns.49 Term and preterm neonates showed evidence of increased postoperative metabolic work, and this increase was correlated with severity of the operation. In the study by Anand et al50 of preterm and term newborns, the most consistent metabolic effect was postoperative hyperglycemia. In that study, the use of anesthesia during surgery on preterm infants was associated with improved outcome. In a subsequent study,51 newborns who received deep anesthesia (high-dose sufentanil) vs lighter anesthesia (halothane and morphine) had a decreased incidence of sepsis, metabolic acidosis, disseminated intravascular coagulation, and death. These neonates also had significantly reduced responses of β-endorphin, norepinephrine, epinephrine, glucagon, aldosterone, and cortisol as well as better insulin responses with less hyperglycemia.

Markers of metabolic and endocrine system activity change in response to stress in the pediatric patient and are affected by analgesic and anesthetic treatment strategies. However, whether pain-induced aberrations in metabolic and endocrine stress responses or, conversely, moderation of the stress response by analgesia directly or indirectly affects host response to infection remains to be explored more closely in pediatric patients.

**OPPORTUNITIES TO DECREASE NOSOCOMIAL INFECTION BY CHOICE OF ANALGESIC REGIMEN**

This critical review highlights the many interrelationships between systems that detect and respond to painful stimuli and those that detect and respond to infectious agents. Surgical patients in general and critically ill infants in particular are at high risk for developing postoperative pain and also for nosocomial infection. Methods to directly boost host immune function in these high-
risk patients have not been successful. Given the multiple interactions between nociceptive and immune pathways, it is intriguing to speculate that better prevention and control of pain might lead to an improvement in host immune function and result in decreased susceptibility to nosocomial infection. Both adult and animal studies suggest that immune function may be enhanced by combined-agent anesthetic and analgesic regimens. However, it remains to be shown whether anesthetics and analgesics have a significant influence on immunomodulation or boost immune function sufficiently to prevent infection.

A major criticism of almost all previous studies relating surgical stress to immune function is the failure to include measurement of pain and anesthetics or analgesics received by the patients. Another major criticism is the lack of longitudinal data to determine if changes in immune function are related to the subsequent incidence of nosocomial infection. Future studies to compare regimens of postoperative analgesia, controlling for procedure, should monitor host immune responses, endocrine and metabolic stress, and pain responses and include follow-up for nosocomial infection.

Our article has summarized the current state of knowledge with regard to interactions between surgical pain and stress and immune function. Although the evidence is still sparse, the continued high risk of nosocomial infection is a compelling reason to explore the nature of these interactions and to test the effects of anesthetic and analgesic strategies to support immune function in critically ill infants and children. Research is urgently needed to determine if the interactions between nociceptive and immune function pathways in critically ill infants and children are similar to those in adults and if host defenses can be enhanced by optimal anesthetic and analgesic strategies. The challenge for researchers and health care professionals in this area is to design robust studies to examine the complex relationship between pain, analgesia, and immune function. For this to be achieved, precise and objective end points of both pain intensity (eg, developmentally appropriate, validated pain scores) and immune function (eg, monocyte HLA-DR antigen) must be used. Choice of analgesia must be based on known mechanisms (eg, nonsteroidal anti-inflammatory agents vs opioids). Finally, adequate patient numbers are required to demonstrate clinical significance. We estimate that such studies may require more than 1000 patients; therefore, this undertaking requires cooperation across multiple sites. Our vision is that future management of pediatric pain will be designed to consider the effect on immune function and will enhance prevention and control of nosocomial infection in children.

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