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Overview

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Abstract

The role of perioperative pain management techniques on immune functions in patients with malignancies is still poorly understood. Although the suppression of cellular and humoral immune response in carcinoma patients is a subject of great scientific interest, we know very little about the changes in innate immunity (natural killer T cells-NKT cells, regulatory T cells-Tregs) following tumor growth, as well as in acquired immunity and cytotoxic functions of NK cells in these patients undergoing surgery and the involvement of different perioperative analgesia techniques. Immune compromise could affect the healing processes, postoperative infections and rate and size of tumor metastases disseminated during operation and may be associated with increased risk of mortality Immunosuppression is also a result of perioperative psychological and physiological stress induced by the mechanisms closely related to hypothalamus-pituitary-adrenocortical axis, sympathetic nervous system, cytokines, opioids and T cell signal molecule. Furthermore, peripheral and central immune reaction play a key role in hyperalgesia and allodynia, as a consequence of releasing proinflammatory cytokines (PIC) from activated microglia and astrocytes. Release of PIC causes the augmented secretion of excitatory neurotransmitters from synaptic nerves of primary afferent neuron, representing PIC as very important mediators of enhanced pain in the periphery and in the central nervous system. These findings emphasise that perioperative pain management in patients with malignancies is significant to attenuate developed serious immune suppression mediated by the complicated network of neuro-immuno-endocrine interactions caused by the primary disease accompanied with exogenous and endogenous stimuli.

INTRODUCTION

Perioperative pain management is one of the most important difficulties that confront surgical patients. Inappropriate pain control may result in a higher incidence of chronic postoperative pain with prolonged hospitalization, augmented postsurgical morbidity and mortality, health care costs, as well as unnecessary suffering of patients *(1)*. Cancer patients represent some of the most sensitive patients for pain control, regarding surgical stress with accompanied suppression of humoral and cellular immunity and diminished number and function of T lymphocytes and natural killer (NK) cells *(2)*. Immunosupression during the perioperative period may be the consequences of opioids and other anaesthetic agents, surgery, blood transfusion, pain, psychological stress and temperature changes, as well as the enhancement of tumor metastasis in experimental conditions *(3),* which suggests that adequate treatment of surgically mediated stress may even help to devoid immunosuppressive effects and represent a protective mechanism

against the metastatic diffusion after cancer surgery *(4)*. Pain can induce neural circuits in the brain and activate brain-controlled pathways to the periphery mediated by hypothalamo-pituitary-adrenal axis and sympathetic nervous system. Neurotransmitters and hormones from these pathways bind receptors which are expressed by immune cells and organs and therefore have the ability to regulate immune response. Overproduction of cortisol additionally leads to cellular immunosuppression *(5)*. Today, the involvement of glia cells incausing pain is marked and drugs which have the possibility of activating glia cells represent powerful mechanisms to induce pain *(6)*.

The role of perioperative pain management techniques on innate and acquired immune response in patients with cancer pain

The immune system distinguishes between multifactor stimuli that allow reaction or rejection to the immunological response. Natural killer (NK) and NK T (NKT) cells are important in innate immune defense. Generally, the appearance of such cells was associated with antitumor and allergic immune response, chronic inflammatory conditions, viral infections and autoimmune diseases. These cells have the unique capacity to rapidly produce large amounts of both T helper: Th1 and Th2 cytokines *(7–10)*. Regulatory T (Treg) cells have active suppression mode and may induce peripheral tolerance *(11)*.

Many cancer-related symptoms (pain, sleep disturbance, fatigue, cognitive dysfunction, etc) are connected with the release of proinflammatory cytokines. These cytokines: interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are released as a part of immune response and may cause a syndrome called sickness behavior which includes depression, lethargy, anorexia, fever, energy conservation, hyperalgesia, etc. *(12, 13)*. It is proposed that cancer-related symptom and the cytokine-induced sickness behavior that develop in animals after the administration of infections or inflammatory agents or proinflammatory cytokines share common cytokine-based neuroimmunologic mechanisms. Cytokines are able to induce signaling that activates glial cells. This interaction is part of an immune network of injury and host that can lead to the development or facilitation of cytokine-related symptoms and pain / depression *(14)*.

During perioperative pain management opioids has shown their immunosuppressive effects. Acute, as well as chronic administration of opioids decreases lymphoproliferation, natural killer (NK) activity, macrophage functions, and the production of interferon-gamma (IFN-γ) and interleukin-2 (IL-2) in experimental animals *(15)*. Opioid administration has been associated with increased susceptibility of animals to bacterial and viral infections, and with decreased survival in tumor-bearing animals. Similar effects have been shown in humans, where data suggest that opioids may have an adverse impact on the immune system *(16)*.

Recently many papers advocate regional anesthesia techniques instead of general anesthesia in carcinoma patients elected for surgery. Regional anesthesia is usually achieved with a combination of local anesthetics and opioids, so the total amount of opioids is reduced regarding general anesthesia as well as their adverse effects on the immune system. Local anesthetics also show anti-inflammatory properties that contribute to better pain control *(17)*. Hong JY and Lim KT 2008 *(18)* showed that pre-emptive epidural analgesia can affect the perioperative immune responses and influence cancer management. Moreover, this analgesia technique is a good method of potentially controlling perioperative immune response and preventing postoperative pain in carcinoma patients.

Aristomenis *et al.* 2008 *(19)* in a retrospective study suggests that paravertebral anesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up. Biki *et al.* 2008 *(20)* compared anesthesia techniques for radical prostatectomy and indicate that the epidural plus general anesthesia group had an estimated 57% (95% confidence interval), 17–78% lower risk of cancer recurrence compared with the general anesthesia plus opioids group, with a corresponding hazard ratio of 0.43 (95% confidence interval).

If we compare the effects on immune responses of morphine and of the atypical opioid analgesic, tramadol, given for postoperative pain, some interesting findings exist. Tramadol and morphine showed similar analgesic function, although tramadol induced an improvement of postoperative immunosuppression and may be preferred to morphine for the treatment of postoperative pain. Morphine and tramadol share the common opioid mechanism of function, but the affinity of tramadol for μ-opioid receptors is lower than that of morphine. On the other hand the antinociceptive effects of tramadol are mediated via a separate, nonopioid mechanism, mediated by the inhibition of neuronal uptake of noradrenaline and serotonin. Maybe these differences are the reason for the diverse pharmacodynamic profile of morphine and tramadol on immune functions *(21, 22)*.

CONCLUSION

Innate and acquired immune responses play a key role in host defense. Patients with malignant diseases have diminished immune functions that can be modulated by surgical stress, pain, tissue injury and invasive micro-organisms which can lead to augmented susceptibility to postoperative infections and therefore difficulties in postoperative recovery. A good choice of perioperative pain management techniques plays an important role in the immune response of patients with malignancies. Prospective trials evaluating the effects of regional analgesia and opioid sparing on cancer recurrence seem warranted.

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