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The Influence of Postoperative Analgesia on the Perioperative Immune Function in Cancer Patients

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Abstract

Postoperative pain significantly suppresses cell-mediated immunity (CMI). Effective postoperative analgesia can improve CMI and reduce cancer recurrence and metastasis. This article reviews the influence of different analgesic agents and techniques on perioperative immune function and long-term outcome of cancer patients, and the underlying mechanisms are described in detail.

Keywords: Postoperative analgesia; Cancer; Perioperative period; Immunity

Introduction

Surgery is the essential and effective treatment strategy for cancer patients. However, surgery per se can suppress perioperative immunity. In which, surgical stress response and postoperative pain are the leading factors. CMI is impaired in cancer patients. Animal studies have shown that postoperative analgesia can attenuate CMI suppression induced by surgery and postoperative pain, consequently reduce the long-term recurrence and metastasis of cancer [1], but similar results from human studies are scarce. Therefore, this review focuses on the possible mechanisms of perioperative CMI suppression and the influence of different postoperative analgesic agents and techniques on CMI and tries to provide an appropriate postoperative analgesic protocol for cancer patients in order to protect CMI and improve the prognosis.

Perioperative cell-mediated immunity

Cell-mediated immunity, in which natural killer (NK) cells and T lymphocytes are involved, plays the predominant role in anti-tumor immunity. Surgical stress and pain have been shown to suppress CMI [2]. NK cells are a subpopulation of large granular lymphocytes; act as the primary defense in perioperative anti-tumor immune mechanisms. NK cells can directly kill cancer cells [3]. In addition, NK cells can eliminate cancer cells by secreting interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and other cytokines [4]. Both animal and human studies confirm that NK cell activity is decreased few hours after surgery, which lasts for several days postoperatively. Data from animal studies suggest an inverse relationship between NK cell activity and cancer metastasis, and this relationship has been demonstrated in patients with breast cancer [5], colorectal cancer [6], lung cancer [7], as well as head and neck cancer [8].

T lymphocytes are involved in regulating the perioperative immune response as the secondary defense. T lymphocytes are classified into helper T cells (Th), cytotoxic T cells (CTL) and suppressor T cells (Tc). Th cells include Th1 and Th2 cell subtypes. Th1 cells mainly secrete interleukin-2 (IL-2), interleukin-12 (IL-12), IFN-γ, and TNF-α, which participate in cell-mediated immunity, whereas Th2 cells produce interleukin-4(IL-4), interleukin-6(IL-6), and interleukin-10(IL-10), which mediate humoral immunity. Several studies have shown that Th1 cell-produced cytokines might increase NK cell activity so as to generate anti-tumor effect, while Th2 cell-produced cytokines can decrease NK cell activity. Under normal circumstances, Th1 and Th2 cells functions are in a dynamic equilibrium. Animal studies have found that perioperative stress response can significantly reduce the Th1/Th2 ratio [9].

The influence of different postoperative analgesic agents on perioperative immune function

Postoperative pain can over activate the central nervous system (CNS) and the hypothalamic-pituitary-adrenaline (HPA) axis, thus, the immune function can be suppressed by the release of endogenous catecholamines, glucocorticoids, prostaglandins and opioid peptides. Catecholamines can activate β2-adrenergic receptors on NK cells and T lymphocytes. In result, NK cell activity is decreased, and Th1 dominant Th1/Th2 equilibrium is shifted to Th2 dominant status. Animal studies have shown that postoperative analgesia can attenuate postoperative pain-induced decrease in host immunity against metastasis [1], on the other hand, postoperative analgesic agents have a direct or indirect negative effect on host immunity.

Opioids

Opioids suppress both cell-mediated and humoral immunity [10]. The mechanism is mediated by opioid receptors, sympathetic nervous system (SNS) and HPA. Morphine can directly activate μ3 opioid receptor on immune cell membrane and increase intracellular calcium level, then, constitutive nitric oxide synthase (cNOS) is activated, and nitric oxide(NO) is generated [11], which may enhance the transcription of inhibitory kappa B alpha(IκBα) and inhibit nuclear factor-κB(NF-κB) to bind with the representative DNA promoter region, as a result, Th1 cell activity is suppressed, and the expression of IFN-γ and IL-2 is decreased [12]. Moreover, opioids indirectly suppress immune function by inhibiting NK cells activity. Morphine activates SNS and HPA pathways, leading to the production of glucocorticoids and catecholamines, the former have negative effect on

immunity, the latter activate adrenergic receptors on NK cell membrane, then, protein kinase A (PKA) is activated by cyclic adenosine monophosphate (cAMP). Activation of cAMP/PKA signaling pathway can ultimately affect the expression of genes and NK cell function by regulating the nuclear transcription factor.

Fentanyl, a synthetic μ-opioid receptor agonist, induces dose-dependent immunosuppressive effect in mice and humans [13,14]. Animal studies have shown that continuous infusion of fentanyl suppresses NK cell activity, lymph proliferation and cytokine production. Furthermore, in the rat model, fentanyl not only inhibits NK cell activity but also promotes cancer metastasis [15].

Those results mentioned above show the immunosuppression of opioids in the absence of pain, while some animal studies suggest that perioperative opioid administration can attenuate surgery-induced immunosuppression by alleviating stress and pain. Perioperative systemic or intrathecal morphine administration not only significantly attenuated surgery-induced inhibition of NK cell activity but also decreased cancer metastasis [16]. The previous results were contradictory, the reason may be, opioids per se exhibit the immunosuppressive effect in the absence of pain, but the immunosuppression caused by surgery is far greater than that of opioids. Opioids can effectively relieve pain and alleviate surgical stress, eventually improve perioperative immune function, which is impaired by surgery. Furthermore, the dosage of opioids reported in those studies was in the clinically related range.

Fortunately, not all the opioids share the immunosuppressive properties. Tramadol, a weak μ-opioid receptor agonist and reuptake inhibitor of norepinephrine and serotonin, does not suppress the immune function. On the contrary, it can increase NK cell activity and facilitate the production of IL-2, and can enhance the proliferation of spleen lymphocytes. In the rat model, tramadol could protect NK cell function and reduce the incidence of cancer metastasis [17]. Moreover, the administration of tramadol 100mg after surgery could increase NK cell activity and promote the recovery of lymphocyte function in uterine cancer patients [18]. The protective effect of tramadol on immune function may be ascribed to its inhibition of 5-HT reuptake [19].

Buprenorphine, the semi-synthetic partial μ-agonist, is a derivative of paramorphine that can be used to control moderate acute pain. Recent studies have found that buprenorphine has no inhibitory effect on immune function. Buprenorphine administered in the rat periaqueductal gray did not alter spleen NK cells, T lymphocytes or macrophages function, while morphine significantly inhibited all the cells function [20]. In the animal studies, when using equianalgesic doses of fentanyl or morphine, only buprenorphine might protect immune function and reduce cancer metastasis induced by surgical stress [21]. In humans, buprenorphine is commonly used to treat opioid addiction as a substitution, and the only available human study showed that buprenorphine was able to improve immune function. When buprenorphine is administered to relieve pain, it does not activate the HPA axis and the SNS [22].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are cyclooxygenase (COX) inhibitors; they not only inhibit prostaglandin synthesis but also have anti-tumor and anti-angiogenic effects. It has been reported that tissue damage or stress can stimulate COX-2 and then, prostaglandin E2 (PGE2) will be produced, which binds E-prostanoid2 (EP2) and EP4 receptors, and inhibits NK cell activity and T lymphocytes proliferation through cAMP/PKA signaling pathway. Recent animal studies have shown that COX-2 inhibitors can prevent morphine-induced cancer growth and metastasis [23]. A retrospective study of 327 patients undergoing breast cancer surgery suggested NSAIDs might reduce the risk of cancer recurrence. One group in this study was given single-dose ketorolac before surgery and the other group received placebo. Long term follow-up results over 5 years found that the breast cancer recurrence rate in ketorolac group was 6%, whereas the rate in the other group was 17%. NSAIDs alone or NSAIDs combined with opioids are widely used in postoperative analgesia, there is still more researches needed to elucidate its impact on immune function in cancer patients in the near future.

α2-adrenoceptor agonists

Clonidine, an α2-adrenoceptor agonist, has been used for postoperative analgesia as well. It exerts analgesic effects mainly through activating α2-adrenergic receptors in spinal dorsal horn to inhibit the release of substance P, and through activating α2 adrenergic receptors in nucleus ceruleus to inhibit nociceptive neurotransmission from dorsal horn neurons. Up to now, few studies have reported the effects of α2-adrenoceptor agonists on perioperative immune function, a recent animal study indicated that clonidine decreased NK cell activity within 24h after operation, however from the 2nd to 8th day postoperatively, NK cell activity recovered gradually to normal level. Furthermore, the lung metastasis of MADB-106 cells in the clonidine group was reduced by 60% [24]. Some researchers believe that α2-adrenoceptor agonists have a dual effect on the stress response. In addition to alleviating pain through central mechanism, α2-adrenoceptor agonists can promote cancer cell apoptosis and the production of anti-inflammatory cytokines. Hence, the results suggest that clonidine may have a positive impact on perioperative CMI as a postoperative analgesic agent.

Local anesthetics

Local anesthetics are the most commonly used drugs in regional anesthesia. Local anesthetics act mainly by blocking sodium ion channels in the neuronal cell membrane. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is terminated. Local anesthetics can inhibit NK cell activity directly in vitro. But a clinical study indicated that the patients receiving perioperative intravenous lidocaine experienced better pain relief postoperatively, and stress-induced immunosuppression was attenuated as well [25]. A large number of clinical data have shown that surgical trauma and postoperative pain can cause significant inflammatory response, and the proinflammatory cytokines including TNF-α, IL-1 and IL-6 are released to a higher level. Postoperative inflammatory reaction is so strong that the immune function will be impaired, and cancer angiogenesis and recurrence will be stumilated [26]. However, experiments in vitro or in vivo have found that lidocaine can generate an anti-inflammatory cytokine effect. With clinically relevant concentration, lidocaine could inhibit cancer cell proliferation and induce apoptosis of breast cancer cells, thereby exert anti-tumor effects [27,28]. These findings suggest that local anesthetics seem to have a protective effect on perioperative immune function.

Effect of postoperative analgesic techniques on perioperative immune function

According to the type of surgery and the degree of postoperative pain, the patients will receive an appropriate postoperative analgesic technique. Regarding cancer patients, more and more scholars believe that different postoperative analgesics will have distinct effects on perioperative immune function and cancer recurrence and metastasis in the long term.

Local anesthetic techniques

Local anesthetic techniques including epidural analgesia, spinal analgesia and peripheral nerve blocks can protect immune function, reduce postoperative cancer recurrence and improve the prognosis. Previous studies indicated that epidural anesthesia provide better control of the surgical stress than general anesthesia. A recent animal study also demonstrated that spinal anesthesia combined with general anesthesia for laparotomy was with a higher Th1/Th2 cells ratio and lower hepatic metastasis of EL4 cells [9]. In humans, only a few retrospective studies illustrated the effects of local anesthetic techniques on long-term cancer recurrence and metastasis. One study revealed that patients who received epidural analgesia after radical prostatectomy had a 57% lower risk of cancer recurrence than patients who received postoperative opioids for analgesia [29]. A retrospective review of medical records identified 143 patients undergoing ovarian serous adenocarcinoma surgery, the 3-year overall survival rates were 78% in the patients who received epidural anesthesia and analgesia, and 58% in the patients who received general anesthesia and intravenous opioid analgesia [30]. The protective effect of local anesthetic technique on perioperative immune function remains unclear, while the possible mechanisms may be attributed to at least three aspects [26]. First, local anesthetic technique provides reliable analgesia through inhibiting noxious stimuli, which is induced by surgery and postoperative pain. Second, the patients who receive local anesthetic technique for postoperative analgesia have lower opioid requirements, while opioids perse can impair the immune function. Third, when local anesthetic technique is used in combination with general anesthesia, the amount of general anesthetics required is reduced. However, several scholars do not consider that the local anesthetic technique can protect the immune function, reduce cancer recurrence or metastasis. In a retrospective study of medical records, patients who underwent radical prostatectomy were randomized to general anesthesia with or without epidural analgesia, the long-term follow-up results demonstrated that there was no significant difference in the two groups for 10-year overall survival ($P = 0.19$) [31]. Another retrospective study found that epidural block for perioperative analgesia was not associated with a decreased cancer recurrence after colorectal cancer surgery ($P = 0.43$) [32]. Most of the clinical evidences regarding the effect of local anesthetic technique on cancer recurrence and metastasis are from retrospective studies till now. Thus, the results possibly lack of reliability. Fortunately, a large prospective clinical study is in progress, and we will look forward to the final results of this study [33].

Other techniques of postoperative analgesia

Cancer patients also receive other techniques and agents for postoperative analgesia, Opioids and NSIADs are primary analgesic drugs. The routes of administration include intravenous, subcutaneous, oral, rectal and parenteral route. Lots of evidences have indicated that traditional opioids such as morphine and fentanyl exert deeper immunosuppression compared to with tramadol and NSAIDs. Therefore, the multimodal analgesic strategy, can provide superior pain relief with fewer side effects, and should be suitable for cancer patients. A randomized controlled study suggested that NSAIDs could reduce the need of morphine [34].

In summary, postoperative pain can suppress the perioperative immune function in cancer patients, and increase the risk of long-term cancer recurrence and metastasis. Animal and human studies have demonstrated that effective postoperative analgesia can improve perioperative immune function, and reduce long-term cancer recurrence and metastasis. Further studies will be needed to elucidate the influence of different analgesic drugs and techniques on perioperative immune function in cancer patients and the underlying mechanisms to provide a more suitable postoperative analgesia protocol in order to protect the immune function and improve the prognosis.

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