THE IMPACT OF REGIONAL ANESTHESIA ON INFLAMMATORY AND STRESS RESPONSE TO SURGERY

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Abstract

The operative trauma triggers an inflammatory response that leads to a series of cascade changes known as the stress response to surgery. During extensive surgical procedures, the development of excessive stress response can result in transient suppression of the immune system. Natural killer cells (NK cells) and Cytotoxic T lymphocytes (CTLs) are the basis of the innate immunity, which is considered the primary defense against the dissemination of malignant cells and infection. One very significant discovery in anesthesiology was that anesthetic treatment can limit the excessive stress response after surgery. It is confirmed that both intravenous lidocaine as a part of a combined anesthesia protocol and regional anesthesia (RA), have positive effects in the reduction of proliferation and migration of malignant cells, as well as in the prevention of excessive and potentially harmful inflammatory reaction and preservation of the innate immunity. Regional anesthesia techniques have already surpassed their primary role in performing operative analgesia. Rather, they are a valuable addition to anesthetic strategy in the prevention of excessive and potentially harmful inflammatory reaction and preservation of the innate immunity.

Aim: we conducted a literature search to identify the most recent available data on the inflammatory and stress responses associated with the use of regional anesthetic techniques. In addition, we also provide our practical experience with these two techniques.

Key words: *inflammation; malignancy; regional anesthesia; stress response; surgery.*

Introduction

Aim: The aim of this educational review is to discuss the most recent literature data, and to take into consideration our experiences regarding the role and the potential benefit of both intravenous lidocaine and regional anesthesia in reducing the stress response and the preservation of innate immunity during surgery in patients with malignant disease.

Methods: A search using PubMed, Google Scholar, EMBASE, and Scopus databases with the terms "regional anesthesia", "stress response", "inflammation", "malignancy" and "surgery" was performed. The most recent articles were reviewed and this review was written relying on the most current information.

1.1 Stress Response to Surgery

The level and magnitude of the stress response and inflammatory reaction are considered proportional to the severity of tissue destruction caused by surgical trauma. The main aim of the secretion of inflammatory mediators (cytokines, chemokines and catecholamines) is the activation of cell-based immunity in order to repair and heal the damaged tissues and organs. However, during extensive and prolonged surgical procedures, we can expect the development of stronger and even excessive stress responses, which can paradoxically produce transient immunosuppression and inhibition of cellular immune elements. Surgical excision of the malignancy inevitably causes significant stress and potential damage to the surrounding tissues that additionally triggers prolonged inflammation in the postoperative period.

The knowledge of the influence of the stress response and inflammation on immune competence derives from research conducted over the past 10 years. One of the pioneers in this field is Horowitz, who introduced the term “inflammatory response syndrome” for the first time in 2015, in order to emphasize the negative impact of the immune suppression on dissemination of malignant cells and infection during surgery. (1) This is particularly important in oncology patients where the rapid division rate of the malignant cells and the hypoxic microenvironment are main stimuli of the inflammatory reaction and secretion of pro-inflammatory cytokines (IL6, IL10, HIFα and VEGF). Changes in the immune function are most profound in the early postoperative period when strong inflammatory response can cause decreased number and lower activity of T lymphocytes. Current data show that impaired innate immunity in any phase of the treatment of malignancy has strong negative prognostic value, in terms of tumor recurrences, metastatic spread as well as overall survival. (2,3)

1.2 Innate Immunity

Although there isn’t a rigid distinction, immune processes are generally divided into innate and adaptive immunity, which regularly intertwine in different clinical scenarios. The primary defense against the dissemination of malignant cells and/or infection is the activity of innate immune cells. These subtypes of T lymphocytes have a natural ability to eliminate malignant, infected, or damaged cells without prior training, memory, or activation. This inherited cytotoxicity is basically the foundation of modern immune-based therapies that are replacing classic cytotoxic therapy. Following initial contact with malignant cells, these groups of T lymphocytes undergo a complex and still not well-understood activation process during which their cytotoxicity increases several times. The main carriers of this T lymphocytes subgroup also called “Innate lymphoid cells - ILCs”, are Natural killer cells – NK cells and Cytotoxic T lymphocytes – CTLs.

1.2.1 NK Cells

NK cells are primarily cytotoxic T lymphocytes that exert a dual mechanism of action against malignant and infected cells. Innate cytotoxicity is mediated through direct lysis of damaged cells via exocytosis of lytic granules containing perforin and granzyme B, as well as through activation of death receptors and induction of genetically programmed cell apoptosis. Additionally, these T lymphocytes are considered the primary source of secretion for the

anti-inflammatory cytokines group (IL2, IL12, IL18 and IFNγ) that oppose pro-inflammatory cytokines and excessive inflammatory reactions. According to the available data, the secretory phase and excretion of cytokines occur after the primary receptor activation period on the surface of NK cells. In the period that follows, NK cells exert direct cytotoxic activation by degranulation of lytic granules and elimination of malignant cells. (4) During the activation phase of the immune cells, a series of morphological and phenotypic changes on NK cells can be detected. Increased cell metabolism is necessary for the rapid increase in cytokines secretion and rise in the anti-inflammatory cytokines concentration, both locally and in circulation. Once activated, NK cells have higher rate of exocytosis of lytic granules and a several-fold increase in cytotoxicity. (5,6)

1.2.2 Cytotoxic T Lymphocytes – CTLs

CTLs are the 2nd active element of the innate immune response that also have a direct cytotoxic activation mechanism. A part from the exocytosis of lytic granules and secretion of perforin and granzyme B, CTLs create direct synapse-like connections with the membranes of malignant and infected cells. Damaged cells can also be eliminated by activating death receptors and initiating genetically programmed apoptosis. The average circulating half-life of NK cells and CTLs is 17 days, however, recent studies have confirmed the existence of long-living NK cells that can be isolated from circulation several months after the initial invasion of the organism. After restimulation, these so-called “memory NK cells and CTLs” have a significantly stronger direct immune response compared to non-stimulated “naive” T lymphocytes. Additionally, research data indicate that memory NK cells and CTLs exhibit cross-reactivity and retain strong cytotoxic potential against malignant cells, even after non-malignant stimulation. These findings are the foundation of modern immunotherapeutic approaches to malignancies that are resistant to standard cytotoxic therapy. (4,7)

During malignant cell elimination, a part from the absolute number of NK cells and CTLs, their activation process that results in increased cytotoxic and secretory function is particularly important. According to the results of experimental and clinical studies, oncology patients who had a lower average number of NK cells and CTLs in the early postoperative period also had a worse prognosis in the final treatment outcome. These patient populations in the 3- and 5-year follow-up period had significantly higher incidence of metastatic spread and recurrence of the malignancy compared to patients with normal or above the average concentration of NK cells and CTLs. (5) The continuous follow-up of the concentration and the activity of T lymphocytes plays an important role in the creation of a prognostic profile during the treatment of patients with different forms of malignancy.

2. The Role of Anesthetic Management and Regional Anesthetic Techniques in Innate Immunity

One of the more significant recent discoveries in anesthesiology is the fact that certain anesthetics and anesthesiology techniques can modulate the severity and duration of the inflammatory response and preserve the immune function. (8-11) Anesthesiology techniques that can limit excessive stress response after surgery include: regional anesthetic techniques,

combined anesthesiology treatment, and non-opioid anesthesia. However, there is only a small number of high-quality randomized clinical studies and the majority of scientific data comes from experimental and in-vitro research that are inconsistent and difficult to translate into clinical recommendations. (12)

Lidocaine is the only amide local anesthetic that is safe for intravenous use in patients. Indications for intravenous use of lidocaine are expanding in recent years as a result of recent findings from clinical and experimental studies. In addition to its primary antiarrhythmic indication, lidocaine is beneficial in controlling and reducing the inflammation and operative stress response. Modern approaches include intravenous lidocaine (i.v. bolus and continuous infusion) in creating an anesthesia protocol based on combined anesthetic strategies. In-vitro and clinical trials have confirmed that lidocaine has a positive effect in reducing proliferation and the invasive potential of malignant cells. Moreover, lidocaine stimulates the cytotoxicity of NK cells in the early postoperative period. (13) Patients treated with continuous intravenous infusion of lidocaine have lower postoperative concentration of pro-inflammatory cytokines (IL1, IL4, IL6, IL10 and VEGF). (14) The impact of lidocaine on the immune system remains a subject of ongoing debates, as 4 activation mechanisms have been identified thus far: 1) apart from the sodium channels, lidocaine also has an inhibitory effect on M_1 muscarine receptors. 2) the anti-inflammatory potential of lidocaine opposes the pro-inflammatory cytokines by inhibiting the Src signal protein that plays a vital role in the destruction of cell membranes and proliferation of malignant population. (15) 3) lidocaine engages in direct interaction with the membranes of NK cells and CTLs and stimulates their cytotoxicity. 4) the analgesic properties of intravenous lidocaine are particularly important, as it create an opioid-saving effect during combined administration of general anesthesia (GA).

There is still no clear consensus on the recommended intravenous dose of lidocaine. For different clinical settings, most authors recommend intravenous bolus dose of lidocaine 1-1.5mg/kg followed by continuous infusion of 1.5-2mg/kg until the end of surgery. The safe therapeutic range for plasma lidocaine concentrations is 1.5-5.0μg/ml, as concentrations >5μg/ml are considered toxic and cause most complications. (16)

Bupivacaine is a local anesthetic used exclusively for epidural, spinal and regional anesthesia (RA). Regional anesthetic techniques are used both as independent techniques and as part of combined general anesthesia. The principal action of RA is the blockade of the sensory neural transmission, thereby providing sufficient analgesia in the affected dermatomes. The additional effect of neuraxial anesthesia and regional techniques is the blockade of the sympathetic transmission that effectively reduces the stress response to the surgical trauma. The damage caused by the surgery triggers neuro-endocrine, metabolic, and inflammatory response, which leads to a series of cascade changes known as the stress response to surgery. In the postoperative period, the end result of these defense mechanisms is suppression of innate immunity and prolonged immunodeficiency, which can be detrimental in oncology patients.

Regional anesthesia techniques (RA) have a great potential in reducing the level of stress response, primarily by blocking the afferent neurotransmission of nociceptive impulses to the

CNS. As RA is performed before surgery and before the occurrence of tissue damage, many authors emphasize this preemptive modality. (17) With the introduction of new and more advanced ultrasound aids, new approaches and safer regional techniques for different operative procedures are emerging. It should be noted that most of the available data regarding the positive effects of RA on inflammatory and stress response come from experimental studies; and implementing these findings into clinical practice remains challenging. In recent years the results of randomized clinical studies comparing the impact of GA and combined anesthesia modalities including RA in different clinical settings were published. Most authors report that the clinical benefits of RA as an analgesia providing tool during surgery or other painful procedures exceeds its primary role. (18-20)

3. Conclusion

The activity of the innate immunity is a natural defense mechanism against the dissemination of malignant cells and the spread of infectious disease. This is especially important during surgeries and in the postoperative period when multiple factors that promote malignancy progression occur. Excessive inflammation and stress response have a detrimental impact on the immune response expressed as a decrease in both concentration and activity of NK cells and CTLs. Regional anesthesia techniques have already significantly extended their role in providing operative analgesia within the corresponding dermatomes. The use of regional anesthetics, both intravenously (lidocaine) or as a nerve plexus block (bupivacaine), is a valuable addition to the anesthesia plan, in terms of preventing the excessive and potentially harmful inflammatory reaction. It is clear that the individualized approach is the future of anesthetic strategy when it comes to applying the most beneficial technique and anesthetic agent for different clinical scenarios. The significance and role of RA in clinical practice remain to be fully established, as additional high-quality, randomized clinical trials across various surgical procedures are needed; however, the immense potential of these techniques is already recognized.

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