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

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Abstract

The operative trauma is triggering an inflammatory response which leads to a series of cascade changes known as stress response to surgery. During extensive surgical procedures the development of excessive stress response can result in transitory suppression of the immune system. Natural killer cells (NK cells) and Cytotoxic T lymphocytes (CTL's) are the base of the innate immunity which is considered the primary defense against 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 combined anesthesia protocol and regional anesthesia (RA), have positive effects in reduction of proliferation and migration of the malignant cells, as well as in prevention of the 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 present valuable addition to anesthetic strategy in prevention of the excessive and potentially harmful inflammatory reaction and preservation of the innate immunity.

Aim: we searched the literature for latest available data regarding the inflammatory and stress response when regional anesthetic techniques are used. We also provide our practical experience with these two techniques from our institution.

Key words: inflammation, malignancy, regional anesthesia, stress response, and surgery.

1. Introduction

Aim: The aim of this educational review was to discuss the latest literature data as well as our experiences about the role and the potential benefit of both intravenous lidocaine and regional anesthesia on reducing the stress response and preservation of innate immunity during the operation of patients with malignant disease.

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

1.1 Stress response to surgery

The level and the magnitude of stress response and inflammatory reaction are considered to be proportional to the severity of the 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 the purpose of the reparation and healing of the damaged tissues and organs. However, during extensive and prolonged surgical procedures we can expect the development of stronger and even excessive stress response which can paradoxically produce transitory suppression of the immune system and inhibition of the cellular immune elements. Surgical excision of the malignancy inevitably causes significant stress and potential damage to the surrounding tissues that is additionally triggering prolonged inflammation in the postoperative period.

The knowledge about the influence of stress response and inflammation on immune competence is coming from research done in the past 10 years. One of the pioneers in this field is Horowitz, who in 2015 for the first time introduced the term “inflammatory response syndrome” 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 are showing 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 dissemination of malignant cells and/or infection is the activity of the cell elements of innate immunity. These subtypes of T lymphocytes have natural ability to eliminate malignant, infected or damaged cells without the need for prior training, memory or activation. This inherited cytotoxicity is basically the foundation of modern immune-based therapies that are taking the place of classic cytotoxic therapy. After the initial contact with malignant cells these groups of T lymphocytes additionally undergo a complex and still not well understood process of activation during which their cytotoxicity increases several times. The main carriers of this subgroup of T lymphocytes also called "Innate lymphoid cells - ILCs", are Natural killer cells – NK cells and Cytotoxic T lymphocytes – CTL's.

1.2.1 NK cells

NK cells are primarily cytotoxic T lymphocytes that have dual mechanism of action against malignant and infected cells. Innate cytotoxicity is performed both by direct lysis of the damaged cells through exocytosis of lytic granules that contain perforin and granzyme B, and by activation of death receptors and induction of genetically programmed cell apoptosis. Additionally, these T lymphocytes are considered the primary source of secretion for the group of anti-inflammatory cytokines (IL2, IL12, IL18 and IFNγ) that are opposing pro-inflammatory cytokines and excessive inflammatory reaction. According to the available data, the secretory phase and excretion of cytokines occur after the period of primary receptor activity on the surface of NK cells. In the following period NK cells are exerting direct cytotoxic activity 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 concentration of anti-inflammatory cytokines both locally and circulatory. Once activated, NK cells have higher rate of exocytosis of lytic granules and multiple increase in their cytotoxicity. (5,6)

1.2.2 Cytotoxic T lymphocytes – CTL's

CTL's are the 2nd active element of the innate immune response that also have direct cytotoxic mechanism of action. Besides exocytosis of lytic granules and secretion of perforin and granzyme B, CTL's are creating direct synapse-like connections with the membranes of the malignant and infected cells. Damaged cells can also be eliminated through activation of the death receptors and initiation of genetically programmed apoptosis. The average circulatory half-life of NK cells and CTL's is 17 days, but recent studies have confirmed the existence of long-living NK cells that can be isolated from circulation several mounts after the initial invasion of the organism. After restimulation, these so-called "memory NK cells and CTL's" have significantly stronger direct immune response compared to non-stimulated "naive" T lymphocytes. Additionally, the research data have shown that memory NK cells and CTL's have cross reactivity and even after non-malignant stimulation have strong cytotoxic potential against

malignant cells. These findings are the foundation of the modern immunotherapeutic approaches of malignancies that are resistant to standard cytotoxic therapy. (4,7)

In the process of elimination of malignant cells, besides the absolute number of NK cells and CTL's, particularly important is the process of their activation resulting in increased cytotoxic and secretory function. According to the results from experimental and clinical studies, oncology patients that in the early postoperative period had lower average number of NK cells and CTL's had 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 CTL's. (5) The continuous follow-up of the concentration and activity of T lymphocytes have important place in the creation of prognostic profile during the treatment of patients with different forms of malignancy.

2. The role of anesthetic management and regional anesthetic techniques on 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 to preserve the immune function. (8-11) Anesthesiology techniques that can limit excessive stress response after surgery are: regional anesthetic techniques, combined anesthesiology treatment and non-opioid anesthesia. However, there are only small number of high quality randomized clinical studies and the majority of scientific data are coming from experimental and in-vitro research that are inconsistent and difficult to be translated into clinical recommendations. (12)

Lidocaine is the only amide local anesthetic that is safe for intravenous use in patients. Indications for i.v. use of lidocaine are expanding in recent years as a result of new knowledge acquired from clinical and experimental studies. In addition to its primary antiarrhythmic indication, lidocaine is useful in control and reduction of inflammation and operative stress response and. Modern approaches are including intravenous lidocaine (i.v. bolus and continuous infusion) in creating an anesthesiology protocol within combined anesthesiology strategies. In-vitro and clinical trials have confirmed that lidocaine have positive effect in reduction of proliferation and invasive potential of the malignant cells, and 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) There are still ongoing debates about the impact of lidocaine on the immune system, as 4 mechanisms of action have so far been identified: 1) Apart from the Sodium channels, lidocaine has also inhibitory effect on M_1 muscarine receptors. 2) Anti-inflammatory potential of lidocaine is opposing the pro-inflammatory cytokines by inhibition of Src signal protein that plays vital role in the destruction of cell membranes and proliferation of malignant population. (15) 3) Lidocaine engages direct interaction with the

membranes of NK cells and CTL's and stimulates their cytotoxicity. 4) Particularly important are analgesic properties of intravenous lidocaine that results in opioid-saving effect during combined GA.

There is still no clear consensus about the recommended i.v. dose of lidocaine. For different clinical settings most of the authors recommend i.v. bolus dose of lidocaine 1-1.5mg/kg followed by continuous infusion of 1.5-2mg/kg until the end of operation. Safe therapeutic range for plasmatic concentrations of lidocaine is 1.5-5.0μg/ml, as concentrations >5μg/ml are considered toxic and responsible for most of the complications. (16)

Bupivacaine is local anesthetic used exclusively for epidural, spinal and regional anesthesia (RA). Regional anesthetic techniques are used both as independent technique and as a part of combined general anesthesia (GA). The 1st association of RA is blockage of the sensitive neural transmission with the effect of providing sufficient analgesia in the corresponding dermatomes. The additional effect of neuraxial anesthesia and regional techniques is the blockage of the sympathetic transmission that is effectively reducing the stress response to the operative trauma. The damage caused by the surgery is triggering neuro-endocrine, metabolic and inflammatory response which leads to a series of cascade changes known as stress response to surgery. In the postoperative period the end result of this defense mechanisms is suppression of the innate immunity and prolonged immunodeficiency that can be detrimental in the oncology patients.

Regional anesthesia techniques (RA) have great potential to reduce the level of stress response primarily by blockage of the afferent neurotransmission of nociceptive impulses to the CNS. As RA is performed before the operation and before the occurrence of tissue damage, a lot of authors are emphasizing this preemptive modality of action. (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 are coming from experimental studies and it presents a challenge to implement this knowledge into clinical practice. 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 are reporting that clinical benefits of RA are far exceeding its primary role as an analgesia providing tool during operation or other painful procedures. (18-20)

3. Conclusion

The activity of the innate immunity is a natural defense mechanism against dissemination of malignant cells and spread of infective disease. This is especially important during operations and in the postoperative period when there are multiple factors that are promoting malignancy progression. Although considered useful and protective mechanism, excessive inflammation and stress response, have detrimental impact on immune response expressed as a decrease in both concentration and activity of NK cells and CTL's. Regional anesthesia techniques have already

significantly surpassed their role in performing operative analgesia in the corresponding dermatomes. The use of regional anesthetics both intravenously (lidocaine) or as a nerve plexus blockage (bupivacaine) present valuable addition to the anesthesia planning in prevention of the excessive and potentially harmful inflammatory reaction. It is clear that the individualized approach is the future of anesthetic strategy in terms of using the most useful technique and anesthetic agent for different clinical scenarios. The significance and the role of RA in clinical practice is still to be determined as more quality and randomized clinical trials are needed for different operation procedures, but it is already accepted that the potential of these techniques is huge.

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