Early immunological events in postoperative epidural/intravenous analgesia after colorectal cancer resection

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Short communication

Early immunological events in postoperative epidural/intravenous analgesia after colorectal cancer resection

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Key words: cellular immunity, colorectal cancer, epidural analgesia, intravenous analgesia, humoral immunity

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Abstract

Background and purpose: *Postoperative pain is a common consequence of extensive surgery with activation of the nervous system for the implementation of pain (nociceptive system), tissue injury or inflammation. As a result of tissue injury, many different mediators are released from damaged tissues, immunocompetent cells, sympathetic and sensory fibers which directly or indirectly activate nociceptors. Postoperative pain leads to suppression of the immune system, including reduced activity of NK cells, cytotoxic T lymphocytes and macrophages.*

Patients and Methods: *We examined the effects of epidural and intravenous analgesia in patients after colorectal cancer surgery on the immune system. We analyzed the phenotype of isolated peripheral blood mononuclear cells of patients during first six postoperative days by flow cytometry and compared them with healthy volunteers.*

Results: *Application of intravenous analgesia leads to statistically significant decreasing in the percentage of cells of innate immunity in comparison with them after epidural analgesia. Intravenous analgesia has led to a statistically significant reduction of subpopulation of T lymphocytes (CD3+) and B lymphocytes (CD19+) on the 6th postoperative day compared to epidural analgesia.*

Conclusion: *Intravenous analgesia after colorectal cancer surgery has led to a statistically significant greater depression of innate and acquired immunity in comparison to epidural analgesia.*

INTRODUCTION

Immune response to the cancer pain is a multimodal, because there is a whole series of interactions between factors, resulting in a complex clinical picture changes *(1–3)*. These changes are due to the action of soluble factors (cytokines, chemokines), activation of hipthalamic--pituitary-adrenal axis (HPA activation) and sympathetic activity (catecholamines) and parasympathetic (acetylcholine) nervous system. Pain leads to activation of the innate and acquired cell immunity *(4–6),* wherein there is a predominance of anti-inflammatory Th2 response (IL-4, IL-10, IL-13), not pro-inflammatory Th1 immune response (IL1-β, IL-2, IL-6, IL-8, IL-12, IFN-γ and TNF-α). Consequently there is a reduction in the number and function of T lymphocytes (helper and cytotoxic T cells), NK cells, NKT cells, reducing the number and function of macrophages and reduced expression of molecules of Major

Histocompatibility Complex II (MHC-II) on the surface of antigen-presenting cells, reduced ability to kill tumor cells and reduced secretion of immunoglobulins (B cells). On the similar way as cancer pain, surgery proceeding simultaneously activates the nervous, endocrine and immune system *(7)*. Brain cortex activates the limbic system, which leads to activation of the hypothalamic periventricular nucleus and activation of HPA axis leading to secretion of cortisol, which reduces the number and function of cells of the innate and acquired immunity through the glucocorticoid receptor *(8, 9)*. Major surgery leads to reflex activation of the sympathetic nervous system (SNS), which stimulates the release of noradrenalin (NA) and adrenaline (A) *(10)*. Immune cells have adrenergic receptors, secretion of NA and A cause immunosuppression *(11)*. Surgical manipulation causes ischemia of organs, which leads to the activation of inflammatory responses; proinflammatory cytokines TNF, interleukins (IL-1 and IL-6) provide further activation of the HPA axis and SNS *(12, 13)*. Some intravenous anesthetics can reduce immunity and it is necessary to be careful when long continuous applications are needed (more than 24 hours), especially when used for postoperative sedation *(14)*. Some inhalation anesthetics may also suppress the immune response *(15)*. Inhibition of ROS (reactive oxygen species), mainly supress the neutrophil function, whose task is to eliminate harmful microorganisms *(16)*. Activated neutrophils are protective alarm for the body because it triggered the initial phase of the inflammatory response *(17)*.

PATIENTS AND METHODS

This study included 80 patients after curative surgery (radical) bowel resection of diagnosed colorectal cancer, committed under general balanced anesthesia. The study also included 30 healthy blood donors as a control group.

Subjects were divided into three groups:

Group I – patients whom after elective surgical resection of colorectal cancer, the pain was treated with intravenous analgesia. Group II –patients whom after elective surgical resection of colorectal cancer, the pain was treated using an epidural analgesia. Group III control –voluntary blood donors.

After the colorectal cancer surgery, patients be placed on the Department of Digestive Surgery, Department of Surgery and Intensive Care Unit, Department of Anesthesiology and Intensive Care, University Hospital Rijeka where were made the continued postoperative treatment in accordance with accepted standards. Postoperative pain was treated to one of the above methods – intravenous or epidural analgesia. Each patient enrolled in the study was taken about 10 ml heparinized venous peripheral blood before surgery, 1st and 6th day after resection of colorectal cancer during intravenous/epidural analgesia. Each patient prior to surgery was familiar with the visual analog pain scale (VAS) that can record the intensity of postoperative pain.

Phenotype of peripheral blood mononuclear cells was determined by flow cytometry on a FACSCalibur flow cytometer (Becton Dickinson, Muantain View, CA, USA). Statistical analysis. data were analyzed using the Statistica 7.0 per Windows. Linear regression equations were generated using a least-squares method and analyzed for differences of covariance.

Statistical significance was calculated by Mann Whitney U test. The differences were considered significant for $p<0.05$.

RESULTS

The data have shown that patients with colorectal cancer have diminished values of immune cells. After operation, during the recovery period in group of patients following epidural analgesia, the percentage of CD3+ cells (T lymphocytes) was augmented at 1st and 6th postoperative day, with statistical significance $p<0,05$ in comparison with the patients underwent intravenous analgesia. The interesting results was also that on the 6th postoperative day, epidural analgesia more than intravenous analgesia significantly augmented B lymphocytes (CD 19+) (Figure 1)

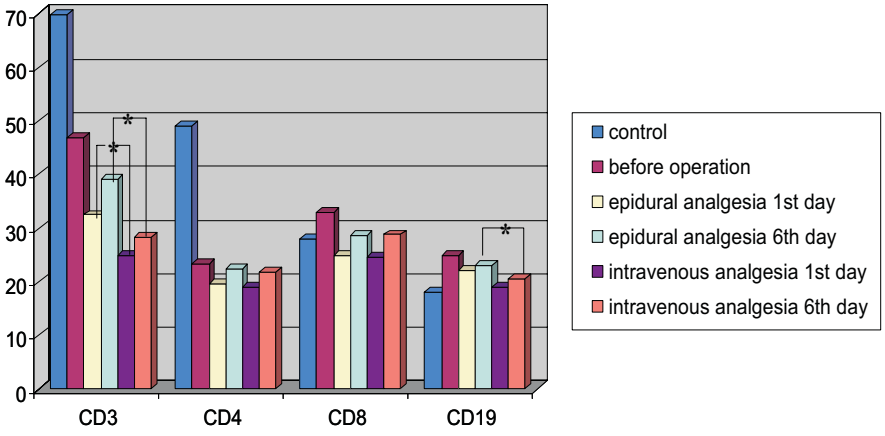

Figure 1. *Changes in phenotype profile of patients underwent epidural/intravenous analgesia after colorectal cancer surgery ($p<0,05$). The percentage of T helper and T cytotoxic cells was not significantlly changed during intravenous analgesia in comparisom with epidural analgesia.*

DISCUSSION

Colorectal cancer is among the most common tumors in humans. According to the frequency of cancer it is in third place (behind lung and breast cancer) and is the second leading cause of mortality in developed countries. The main goal of modern analgesia is that without taking consciousness prevents physiological stress response to surgical injury, which is reflected in significant hemodynamic, metabolic and neuroimmunological changes in the body *(18)*. Epidural analgesia prevents stress response inhibiting transmission of nerve impulses from their sources using local anesthetic with or without combination with opiates or opioids *(19)*. The data emphasize that during the postoperative pain management, epidural analgesia more than intravenous, prevents some immune dysfunctions, contributing to the more efficient postoperative recovery than the patients undergoing intravenous analgesia. The advantages of the epidural space are the ability to perform segmental blocks, and anesthetized and make analgesia in dermatome only at the level of surgical intervention. This concept is most commonly use for a combination of balanced general anesthesia with epidural analgesia during surgery, after which the epidural catheter introduced during operation, permanently stay and we may continue intermittent epidural analgesia *(20)*. Patients with malignancies have decreased immune response, which may very often be additionally disrupted with intensive pain and modulate with appropriate pain management techniques *(21–23)*. Although there are controversial data in the literature, the large studies, which included more than 1,400 subjects, indicated that the postoperative epidural analgesia showed statistically significantly more effective in combating pain than parenteral administration of opioids *(24)*. Our results showed a significantly lower immunosuppression caused by epidural analgesia compared with the effect of intravenous analgesia in perioperative period in patients after resection of colorectal cancer. We may conclude that the selections of appropriate methods of analgesia are invaluable for the postoperative period of reconvalescency.

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REFERENCES

1. ANISMAN H, MERALI Z 2003 Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med 35:* 2–11
2. HERMAN J P, OSTRANDER M M, MUELLER N K, FIGUEIREDO H 2005 Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry 29:* 1201–13
3. MIGNINI F, STRECCIONI V, AMENTA F 2003 Autonomic innervation of immune organs and neuroimmune modulation. *Auton Autacoid Pharmacol 23:* 1–25
4. ELENKOV I J, CHROUSOS G P 2002 Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann N Y Acad Sci 966:* 290–303
5. MUELLER D L 2003 Tuning the immune system: competing positive and negative feedback loops. *Nat Immunol 4:* 210–1
6. VIVEROS-PAREDES J M, PUEBLA-PEREZ A M, GUTIERREZ--CORONADO O, SANDOVAL-RAMIREZ L, VILLASENOR--GARCIA M M 2006 Dysregulation of the Th1/Th2 cytokine profile is associated with immunosuppression induced by hypothalamic--pituitary-adrenal axis activation in mice. *Int Immunopharmacol 6:* 774–81
7. CHAPMAN R C, TUCKETT R P, SONG W C 2008 Pain and Stress in a Systems Perspective: Reciprocal Neural, Endocrine and Immune Interactions. *J Pain 9:* 122–45
8. CZURA C J, TRACEY K J 2005 Autonomic neural regulation of immunity. *J Intern Med 257:* 156–66
9. KUROSAWA S, KATO M 2008 Anesthetics, immune cells, and immune responses. *J Anesth 22:* 263–77
10. BENARROCH E E 2006 Pain-autonomic interactions. *Neurol Sci 27:* 130–3
11. BLANDINO P JR. BARNUM C J, DEAK T 2006 The involvement of norepinephrine and microglia in hypothalamic and splenic IL-1beta responses to stress. *J Neuroimmunol 173:* 87–95
12. CECILIANI F, GIORDANO A, SPAGNOLO V 2002 The systemic reaction during inflammation: the acute-phase proteins. *Protein Pept Lett 9:* 211–23
13. DUNN A J 2000 Cytokine activation of the HPA axis. *Ann N Y Acad Sci 917:* 608–17
14. KELBEL I, WEISS M 2001 Anestethic and immune function. *Curr Opin Anaesthesiol 14:* 685–91
15. TSCHAIKOWSKY K, RITTER J, SCHROPPEL K, KUHN M 2000 Volatile anesthetics differentially affect immunostimulated expression of inducible nitric oxide synthase: role of intracellular calcium. *Anestesiology 92:* 1093–102
16. KEVIN L G, NOVALIJA E, STOWE D F 2005 Reactive oxygen species as mediators of cariac injury and protection: the relevance to anesthesia practice. *Anest Analg 101:* 1275–87
17. HU G, VINTEN-JOHANSEN J, SALEM M R, ZHAO Z Q, Crystal G J 2002 Isoflurane inhibits neutrophil-endothelium interactions in the coronary circulation: lack of role for adenosine triphosphate-sesitive potassium channels. *Anest Analg 94:* 849–56
18. DAHL J B, KEHTLET H 2006 Postoperative pain and its management. U: McMahon SB, Koltzenburg M, ur. Wall and Melzack's textbook of pain. Elsevier Churchill Livingstone, Philadelphia, p 635–51
19. CREWS J C, HORD A H, DENSON D D, SCHATZMANN C 1999 A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.0005% morphine alone fot the management of postoperative paine in patients undergoing major abdominal surgery. *Anesth Analg 89:* 1504–9
20. WHITE P F 2008 Multimodal analgesia: its role of preventing postoperative pain. *Curr Opin Investig Drugs 9:* 76–82
21. GOLUBOVIC V, GOLUBOVIC S, SOTOSEK-TOKMADZIC V, MRAKOVCIC-SUTIC I 2009 Immune response in patients with cancer pain. *Period biol 111 (2):* 223–225
22. MRAKOVCIĆ-SUTIĆ I, BACIĆ D, GOLUBOVIĆ S, BACIĆ R, MARINOVIĆ M 2011 Cross-talk between NKT and regulatory T cells (Tregs) in modulation of immune response in patients with colorectal cancer following different pain management techniques. *Coll Antropol 35 (2):* 57–60
23. BACIĆ D, URAVIĆ M, BACIĆ R, SUTIĆ I, PETROSIĆ N 2011 Augmentation of regulatory T cells (CD4+CD25+Foxp3+) correlates with tumor stage in patients with colorectal cancer. *Coll Antropol 35 (2):* 65–8
24. BLOCK B M, LIU S S, ROWLINGSON A J, COWAN A R, COWAN J A JR, WU C L 2003 Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 290: 2455–63