Received: 13.03.2013 / **Accepted:** 20.05.2013
DOI: 10.5137/1019-5149.JTN.8218-13.0

How Analgesia-Sedation Alters Monocyte mCD14 and HLA-DR Levels in Patients Undergoing Cerebral Angiography?

Serebral Anjiyografi Yapılan Hastalarda Analjezi-Sedasyon mCD14 ve HLA-DR Seviyelerini Nasıl Değiştirir?

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ABSTRACT

AIM: This study aims to evaluate how analgesia-sedation causes alterations of HLA-DR and cytokines (IL-10 and IL-6) in patients undergoing cerebral angiography for several cerebral vascular diseases.

MATERIAL and METHODS: This study includes 41 males who underwent cerebral angiography. The study sample was divided into two: Group I had 7 patients who did not receive and group II had 34 patients who received analgesia-sedation before cerebral angiography. A venous blood sample was collected before and after cerebral angiography.

RESULTS: Analgesia-sedation caused significant increase CD4+ and CD19 T lymphocytes ($p < 0.001$) but group I showed significant increase in CD40, CD154, and MHC-II levels ($p < 0.001$) after cerebral angiography.

CONCLUSION: We suggest that the effects of fentanyl and midazolam on the immune response are the reflection of the effects by the monocyte, mHLA-DR expression. In the future, depending on the immunological status of the patients, different anesthetic applications including the new anesthetic agents that will be able to decrease immune system suppression will be required.

KEYWORDS: Analgesia, Anesthesia, HLA-DR, Monocyte, Sedation

ÖZ

AMAÇ: Bu çalışmanın amacı, çeşitli serebral hastalıklar nedeni ile serebral anjiyografi yapılan hastalarda analjezi-sedasyonun HLA-DR ve sitokinleri (IL-10 ve IL-6) nasıl değiştirdiklerini ortaya koymaktır.

YÖNTEM ve GEREÇLER: Bu çalışma, serebral anjiyografi yapılan 41 erkek olguyu içermektedir. Çalışma örneği 2 gruba ayrıldı: Grup I 7 olguyu içermekte olup analjezi-sedasyon almayan ve grup II ise 34 olguyu içerip cerebral anjiyografi öncesi analjezi-sedasyon alanlardan oluşmuştur. Serebral anjiyografi öncesi ve sonrası venöz kan örnekleri alınmıştır.

BULGULAR: Serebral anjiyografi sonrası analjezi-sedasyon grup I'de anlamlı olarak CD4+ and CD19 T lenfositlerinin artmasına sebep olmuştur ($p < 0.001$) fakat grup II'de anlamlı olarak CD40, CD154, and MHC-II seviyeleri artmıştır ($p < 0.001$). DSA sonrası her iki grup karşılaştırıldığında grup II CD4+ ve CD19 lenfositlerinin anlamlı arttığını ($p < 0.001$) gösterirken grup I'de CD40, CD154 ve MHC-II seviyeleri anlamlı artış göstermiştir ($p < 0.001$).

SONUÇ: Fentanil ve midazolamın bağışıklık yanıt üzerine olan etkilerinin mHLA-DR'nin yansıması olduğunu düşünüyoruz. Gelecekte, hastanın bağışıklık durumuna bağlı olarak bağışıkşıl sistemi baskılanmasını azaltıcı etkileri olan yeni anestetik ajanları da içeren farklı anestetik uygulamalar gerekecektir.

ANAHTAR SÖZCÜKLER: Analjezi, Anestezi, HLA-DR, Monosit, Sedasyon

INTRODUCTION

It is well-known that any trauma including invasive procedures to the body can cause alterations in the immune system The changes in the response of the immune system to any stress may complicate the clinical status of the patient from anxiety to severe medical complications (8, 14). Digital subtraction angiography (DSA) is one of the most frequent invasive procedures performed in the neuroradiology departments with the collaboration of neurosurgeons for several reasons, especially for vascular lesions, and this procedure is also an trauma to the body leading to stress. In case of stress that may be due to any invasive intervention such as DSA, the immune system has to make some alterations in order to defend the body (1, 16). During the invasive procedures,

patients are given anesthetic drugs that may directly affect the immunocompetent cells, and the potential effects of anesthetic agents on the immune system are a constant focus of the attention in the field of anesthesia in recent years. Studies on immunity following the combination of anesthesia and surgical stress have yielded conflicting results (6). Monocytes are important in immune reactions such as cytokine production and antigen presentation. Monocyte and macrophage development us affected by the secretion of the cytokines, lymphokines and interferons by activated T lymphocytes (9). Expression of human leukocyte antigen-DR (HLA-DR) is considered a significant indicator of the immune response because of the important role that HLA-DR plays in presenting antigen to T-lymphocytes. However the effects of anesthetic agents on cytokine production and monocyte surface receptor expression are still unclear (2). In this journal we had demonstrated the effects of analgesia-sedation on the immune system in a group of patients undergoing DSA and the results had shown that analgesia-sedation before DSA causes increase in the levels of some cytokines and lymphocytes (CD56-natural killer cell) and we suggested that either reducing or stopping the actions of the cytokines may decrease unwanted effects of inflammation after any invasive intervention (17).

In this paper in the same group of patients (17) we sought the alterations of monocyte membrane surface receptor CD14, human leukocyte antigen (HLA)-DR and cytokines (IL-10 and IL-6) after DSA.

MATERIAL and METHODS

This work was conducted at the Departments of Physiology and Neurosurgery, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul. Since this study is one of the parts of our previously published work (17), detailed material and methods and sample collection and handling will not be repeated here. The readers should refer to our previously published work for detailed information (17).

Statistical Analysis

All data collected from the patients were organized in a database (Excel, Microsoft Corp.). Numeric variables were provided as the mean ± SD. For statistical analysis, we used "paired sample t test" for the comparisons of the values between before and after cerebral DSA for the same group. For the comparisons between group I and II before and after cerebral DSA, the non-parametric "independent sample t test" was used. A probability value less than 0.05 was considered statistically significant. All statistical calculations were performed using commercially available software (SPSS version 12.0, SPSS Inc.).

RESULTS

Due to the large amount of data obtained, the parameters reported below are those which were found to be significant ($p<0.05$) and the all the comparisons are given in figure-1 through 8 in summary.

When the group I was compared to its control values, we found that cytokines (IL-6 and -10) showed significant increase after DSA ($p < 0.01$) and no change was noted in the monocyte and lymphocyte levels (Figure 1). Regarding the group II, after DSA lymphocytes and cytokines had significantly higher levels ($p < 0.01$) but monocytes showed lower levels ($p < 0.01$) compared to its controls (Figure 2).

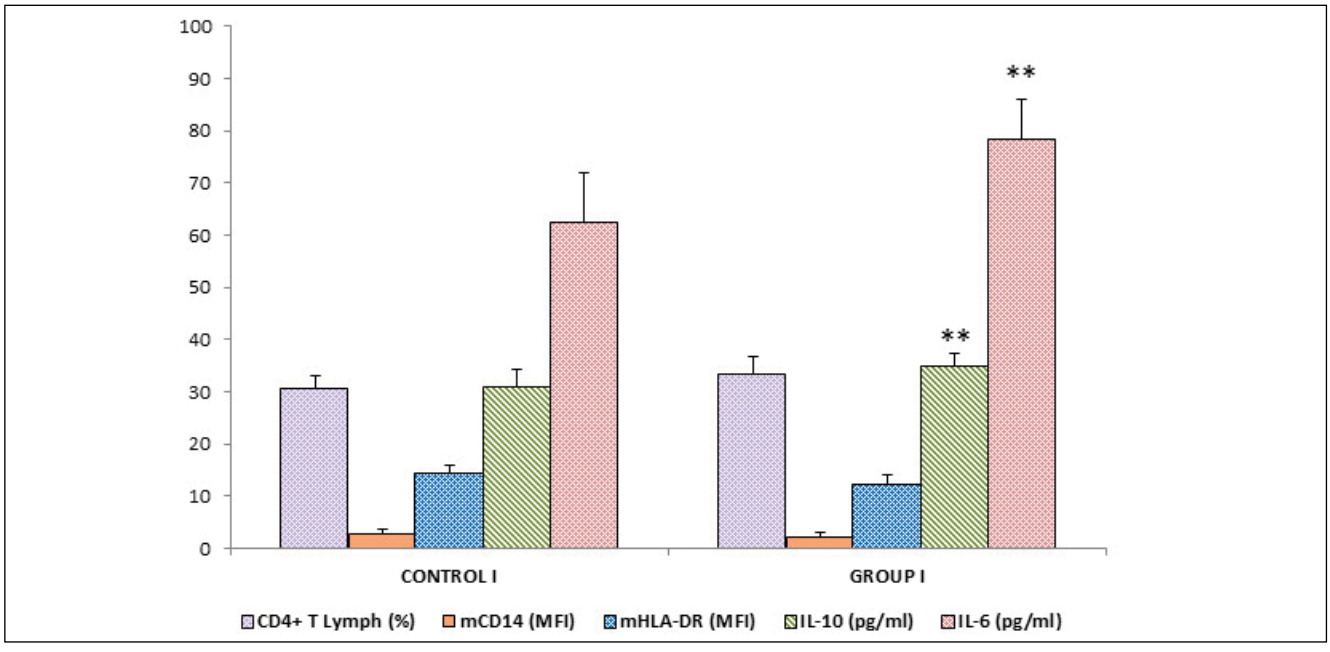

Figure 1: Group I (patients without analgesia-sedation) showed higher levels of the cytokines after DSA including IL-6 and IL-10 compared to the controls.

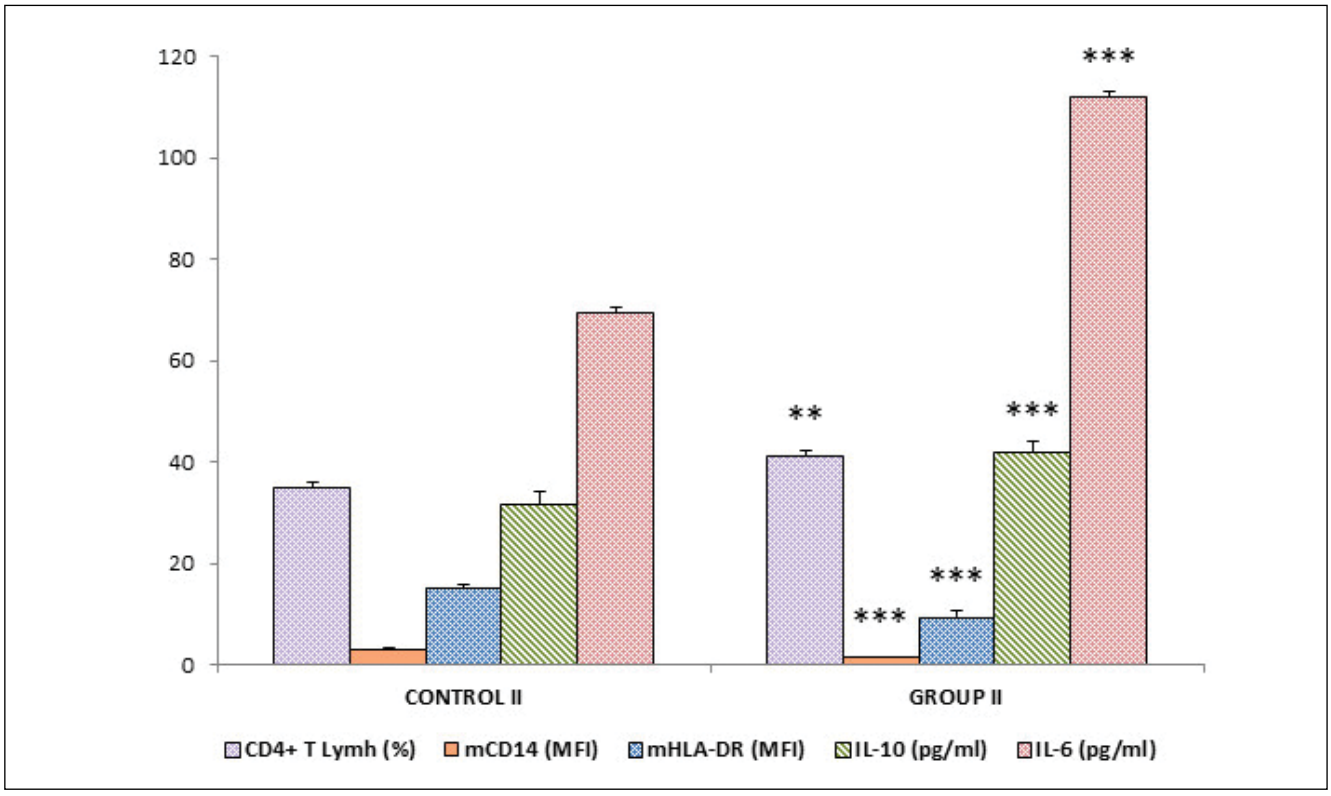

Figure 2: Group II (patients with analgesia-sedation) showed significantly lower levels of CD14 and HLA-DR while other parameters were found to be higher in group II compared to its controls.

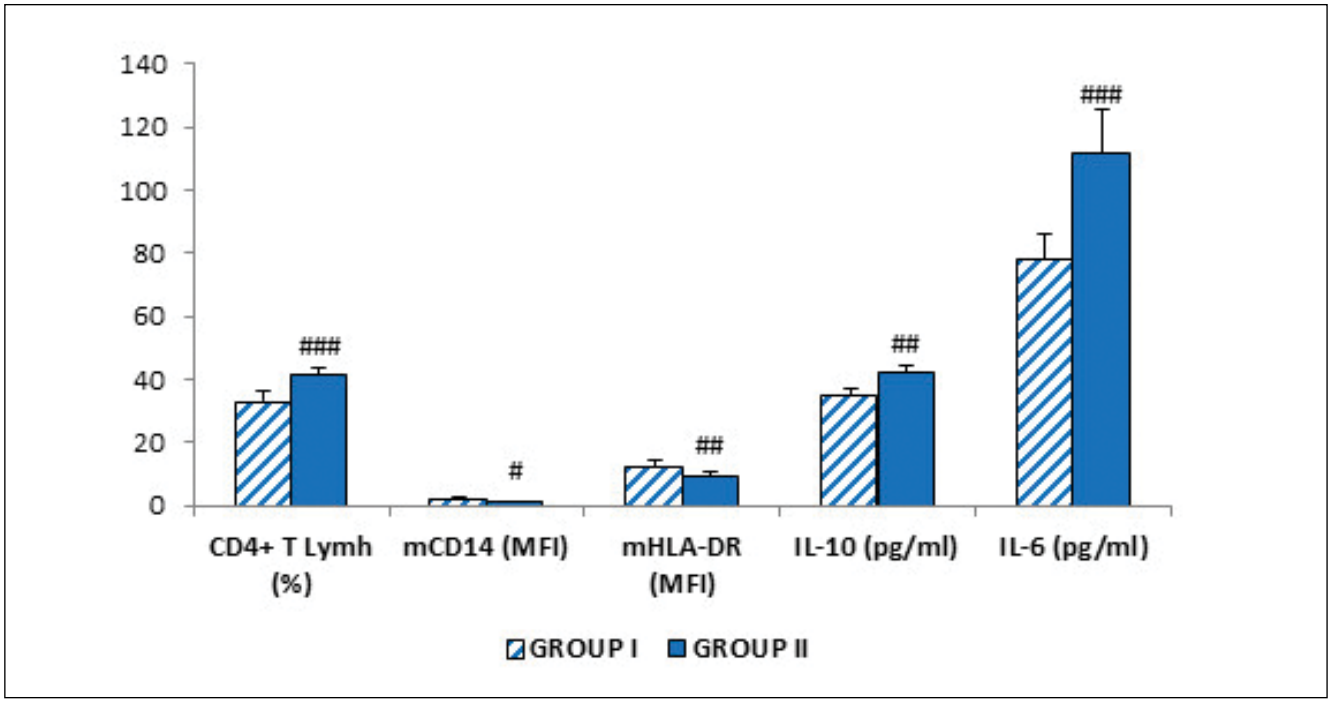

Figure 3: This figure shows significantly higher levels of CD4+ T lymphocytes, IL-6 and IL-10 in group II compared to group I. However, CD14 and HLA-DR levels were significantly lower in group II.

Comparing the two groups demonstrated that CD4+ T lymphocytes and IL-6 levels increased very significantly ($p < 0.001$) and IL-10 levels significantly ($p < 0.01$) in the group II but MC14 and HLA-DR levels ($p < 0.01$) decreased significantly in the same group (Figure 3).

DISCUSSION

Surgical stress including invasive DSA induces hemodynamic, metabolic, neuro-humoral and immune complex of the body and the magnitude of induction and resulting changes depend on the magnitude of stress in the peroperative or per-procedural period. The natural response of the body to stress such as surgical trauma is generated by the main cells of compensatory anti-inflammatory or immune-suppressive systems. Surgical stress leads the body to have activated immune mechanisms that at the same time induces adaptive immune responses (11, 16). Blood vessels become the center of the immune reactions with the help of several endogenous and exogenous stimulations in the tissue. On the other hand, defensive reactions occurring cause micro-trauma to the tissue and repair of the tissue at the same time begins in order to eliminate the harmful effects of the micro-trauma.

In the English literature, we did not encounter any study demonstrating reactive changes related to inflammation and the immune system after DSA. Current work for the first time shows that IL-10 had rapid increase in both group and we think that this increase resulted in slowdown or reduction in the immune response (12). Major histocompatibility complex-II (MHC) molecules have a critical role in the functions and regulations of the immune system. The main role of MHC molecules is to present foreign proteins fragments to antigen specific cells by binding the peptid fragments. Primary MHC class II molecules are the monocytes, macrophages, dendritic cells and B cells. These cells lead CD4+ T cells to recognize the extracellular proteins and to regulate the immune response by cytokines. In the present study, the monocyte, mCD14 and HLA-DR (MHC class II molecule) that play a central role in the initiation of the immune response and presenting antigen to the lymphocytes, decreased significantly in the group that received sedation after the DSA (18). But the level of CD4+ lymphocyte increased notably. Decrease in monocyte and HLA-DR levels may be related to the increase in the risk of severe development of sepsis (3, 7, 18). Loss of HLA-DR on the cell surface results in impairment of T cell function that may decrease the capacity of the monocytes to present antigen. An *in vitro* study emphasizes that IL-10 regulates mHLA-DR expressions (4). It has been demonstrated that IL-6 and mCD14 expressions downregulate while IL-10 upregulates the monocytes, mHLA-DR (15). In the present study while IL-10 concentration increased in the plasma, mCD14 and mHLA-DR expressions decreased because of the effects of the surgical trauma, here DSA and anesthesia. Although CD4+ T lymphocytes which are the major source of IL-10, showed increase in patients received analgesia-sedation, levels of mCD14 was observed. Increase in TH2 cytokines including IL-6 and IL-10 can be considered as a property of stress due to DSA and anesthesia given. However, this finding is a matter of debate. The activation of IL-10 is a natural result of inhibition of the excessive inflammatory response (10) and this inhibitory property may increase susceptibility to sepsis. The mechanism(s) of the monocyte, mCD14 suppression is not clear but it is regulated by IL-10. Surgical stress increases IL-6 response and this increase may be related to the initiation of severe infection and finally sepsis (5, 13).

CONCLUSION

In conclusion, our results suggest that the effects of fentanyl and midazolam on the immune response are the reflection of the effects by the monocytes and mHLA-DR expression. We demonstrated significant suppression of mCD14 and HLA-DR expressions in those who received analgesia-sedation and both high IL-10 and IL-6 contribute to this suppression. These findings may explain the degradation of some mechanisms of host immune system. The long-term prognosis of the patients who underwent surgical intervention is important because immunomodulator effects of anesthetic agents are a double-edged sword: immunosupression may either be beneficial or harmful. By proper selection of anesthetic agents, the negative effects regarding immunosuppression may be lessened the risk of infection during postprocedural periods. Nonetheless, the anti-inflammatory effects of anesthetic agents may be a beneficial treatment modality in case of ischemia-reperfusion injury. In the future, depending on the immunological status of the patients, different anesthetic applications including the new anesthetic agents that will be able to decrease immune system suppression will be required. In order to have this end, future prospective studies are needed for the explanation of the relations between the immune system and anesthetic agents.

REREFENCES

1. Bauer M, Rensing H, Ziegenfuss T: Anesthesia and perioperative immune function. Anesthetist 47: 538-556, 1998
2. Benjamini E, Leshowitz S: Immunology, a short course. New York: Wiley-Niss Inc. 1991:175-182
3. Cardinale F, Chinellato I, Caimmi S, Peroni DG, Franceschini F, Miraglia Del Giudice M, Bernardini R: Perioperative period: Immunological modifications. Int J Immunopathol Pharmacol 24 (Suppl 3):S3-12, 2011
4. de Waal Malefyt R, Haanen J, Spits H, Roncarolo MG, te Velde A, Figdor C, Johnson K, Kastelein R, Yssel H, de Vries JE: Interleukin 10 and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-presenting capacity of monocytes via downregulation of class 2 major histocompatibility complex expression. J Exp Med 174: 915-924, 1991
5. Desborough JP: The stress response to trauma and surgery. Br J Anaesth 85: 109-117, 2000
6. Griffis CA, Page G, Kremer M, Yermal S: Implications of immune function to anesthesia care. AANA J 76: 449-454, 2008

7. Hershman MJ, Cheadle WG, Wellhausen SR, Davidson PF, Polk HC Jr: Monocyte HLA-DR antigen expression characterizes clinical outcome in trauma patient. Br J Surg 77: 204-207, 1990
8. Levine S, Ursin H: What is stres? In: Brown MR, Koob GF, Rivier C, (eds), Stress: Neurobiology and Neuroendocrinology. New York: Dekker, 1991:3-21
9. Lewis L: Cells of the immune response: Lymphocytes and mononuclear phagocytes. In: Stites DP, Terr AI (eds), Basic and Clinical Immunology. London: Appleton and Lange, 1999: 61-72
10. Lyons A, Kelly JL, Rodrick ML, Mannick JA, Lederer JA: Major injury induces increased production of interleukin-10 by cells of the immune system with a negative impact on resistance to infection. Ann Surg 226: 450-460, 1997
11. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, Moutardier V, Blache JL: Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): Early markers of postoperative sepsis after major surgery. Br J Anaesth 94: 767-773, 2005
12. Ogata M, Okamoto K, Kohriyama K, Kawasaki T, Itoh H, Shigematsu A: A role of interleukin-10 on hyporesponsiveness of endotoxin during surgery. Crit Care Med 28: 3166-3170, 2000
13. Salo M: Effects of anaesthesia and surgery on the immune response. Acta Anaesthesiol Scand 36: 201-20, 1992
14. Schneider N, Schedlowski M, Schürmeyer TH, Becker H: Stres reduction through music in patients undergoing cerebral angiography. Neuroradiology 43: 472-476, 2001
15. Spittler A, Willheim M, Leutmezer F, Ohler R, Krugluger W, Reissner C, Lucas T, Brodowicz T, Roth E, Boltz-Nitulescu G: Effects of 1 alpha, 25-dihydroxyvitamin D3 and cytokines on the expression of MHC antigens, complement receptors and other antigens on human blood monocytes and U937 cells: Role in cell differentiation, activation and phagocytosis. Immunology 90: 286-93, 1997
16. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson HC: The effect of anesthetic agents on the human immune response. Anesthesiology 72: 542-552, 1990
17. Tureci E, Kızılkilic O, Akyol S, Pekel F, Tanriverdi T, Hanci M, Bahar M: The effects of analgesia-sedation on the immune system before and after cerebral digital subtraction angiography. Turk Neurosurg 21: 340-346, 2011
18. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ: Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. Br J Surg 80: 205-209,1993