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The Effects of Analgesia-Sedation on the Immune System before and after Cerebral Digital Subtraction Angiography

Serebral Dijital Subtraksiyon Anjiyografi Öncesi ve Sonrası Analjezi-Sedasyonun İmmün Sistem Üzerine Etkileri

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ABSTRACT

AIM: Cerebral digital subtraction angiography (DSA) is an invasive procedure and may cause inflammatory responses in the body. This study aims to provide cytokine and lymphocyte profile in a population of patients underwent cerebral DSA.

MATERIAL and METHODS: Forty-one male patients who admitted for cerebral DSA were included in this study. Patients were divided into two groups: Group I (n = 7) included patients who did not receive analgesia-sedation and group II (n = 34) received analgesia-sedation before procedure. For the molecules, a venous blood samples from every patient was collected before and after cerebral DSA.

RESULTS: Cytokine levels in group I showed a trend to increase in the majority of the molecules after the procedure except IL-1β. In group II, cytokines showed variable trend. When comparing the two groups regarding cytokine levels after cerebral DSA, IL-1β, IL-10, IL-12, and IFN-γ levels increased significantly in group II. Comparing the two groups with respect to lymphocytes after cerebral DSA showed that CD56 levels were significantly higher in group II and other parameters did not show significant differences.

CONCLUSION: It can be possible that delimitation of the action(s) of the cytokines affecting the secretion or activation of CD56 (natural killer) may avoid complications of inflammation after invasive procedures.

KEYWORDS: Angiography, Cerebrum, Cytokine, Inflammation, Lymphocytes, Immune system

ÖZ

AMAÇ: Serebral dijital subtraksiyon anjiyografi (DSA) invasiv bir işlemdir ve vücutta inflamatuvar yanıta neden olabilir. Bu çalışmanın amacı serebral DSA için başvuran hastaların sitokin ve lenfosit profillerini ortaya koymaktır.

YÖNTEM ve GEREÇ: Çalışmaya serebral DSA yapırmak üzere başvuran 41 erkek hasta dahil edilmiştir. Hastalar iki gruba ayrılmıştır: Grup I (n = 7) işlem öncesi analjezi-sedasyon almayan ve grup II (n = 34) analjezi-sedasyon alan hastalardan oluşmuştur. Her hastadan serebral DSA işlem öncesi ve sonrası moleküllerin çalışılması amacı ile venöz kan örnekleri alınmıştır.

BULGULAR: Grup I'de işlem öncesi bakılan sitokinlerin çoğunluğunda IL-1β hariç artış eğilimi görüldü. Grup II'de ise seviyeler değişkenlik gösterdi. Serebral DSA sonrası iki grup karşılaştırıldıklarında IL-1β, IL-10, IL-12 ve IFN-γ seviyeleri grup II'de anlamlı olarak yüksek bulundu. İki grubun serebral DSA sonrası lenfosit molekülleri karşılşatırıldıklarında grup II'de CD56 seviyeleri anlamlı olarak yüksek bulundu ve diğer parametrelerde fark saptanmadı.

SONUÇ: Sonuçlara dayanarak, CD56 (doğal öldürücüler) aktivitesini veya sekresyonunu artıran sitokin fonksiyonlarının baskılanması ile işlem sonrası gelişebilecek olan inflamatuvar komplikasyonlardan kaçınılabilinir. Bunun ortaya konması daha fazla sayıda hasta içeren ileri çalışmaları gerektirmektedir.

ANAHTAR SÖZCÜKLER: Anjiyografi, Serebrum, Sitokin, Inflamasyon, Lenfosit, İmmün sistem

INTRODUCTION

It is clearly known that any intervention causing stress to patients activates different neurophysiologic systems which result in stress response. The changes in the body as a response to stress following intervention may complicate the patients' current clinical picture which may range from anxiety to severe medical complications (9, 15). One of the most common interventions in medical practice is the application of digital subtraction angiography (DSA) which has mainly been used in the diagnosis and treatment of certain intracranial vascular pathologies since the first application of cerebral DSA by Egas Moniz in 1927 (11). Although it is not a surgical intervention, it generally causes stress in patients because of its invasiveness (12). During the procedure, the role of anesthesiology becomes apparent that anesthetic agents are given to sedate patients in order for cerebral DSA to be performed safely. However; it has been demonstrated that anesthetic agents given during any procedure may lead to immunosuppression (7). The negative effects of surgical trauma on the immune system may alter patients' clinical status which prolongs intensive care unit stay. In every surgical or invasive procedure resulting in changes in the immune system, the precise balance between pro- and anti-inflammatory cytokines should be maintained in order to get optimum results in terms of patient's well-being. On the one hand suppression of excessive release of pro-inflammatory mediators could be beneficial to prevent further tissue damage such as in systemic inflammatory syndrome (SIRS) or ischemia-reperfusion injury. But on the other hand, it has been well-known that suppression of the inflammatory response more than required may result in multiple organ insufficiency and septic shock which may be lethal (8).

The aim of this prospective clinical study was to observe how analgesia-sedation affects the cells and their cytokines of specific and non-specific immune systems in patients who undergone cerebral DSA for either the diagnosis or treatment of intracranial vascular pathologies.

MATERIAL and METHODS

Study groups

This work was conducted at the Departments of Physiology and Radiology (section of Neuroradiology), Cerrahpaşa Medical Faculty, Istanbul University, İstanbul. A total of 41 male patients who needed to have cerebral DSA and admitted to the clinic of neuroradiology were included in this study. All patients were in ASA I [healthy (American Society of Anesthesiology Classification)] and the age ranged from 35 to 60 years.

Selection criteria for the subjects are as follows: patients who had 1) normal electrocardiography (ECG); 2) normal chest x-ray; 3) normal blood, urine and coagulation tests; and 4) no history of prolonged used of any drug and of allergy. The group was divided into two subgroups. In group I, seven patients who were not given analgesia-sedation were included while thirty-four patients who had analgesia-sedation before and after cerebral DSA were included in group II. Before and after DSA a sample of blood from venous line for the purpose of the study was collected from each patient. All the procedures including cerebral DSA were performed after receiving written informed consent from either the patients or the next of kin.

Sample handling and anesthesia

Every patient was on none per oral (NPO) for 6 hours and had 8 hours sleep before the procedure. All patients were taken to the preparing room in which room temperature was 20-22 °C and all disturbing causes that might have resulted in stress were eliminated and patients took rest for 30 to 45 minutes before cerebral DSA. Then 5 mL of blood samples were taken twice to the two tubes with ethylenediaminetetraacetic acid (EDTA) (from both group I and II). About 4 to 5 hours later from the first blood sample was taken, patients were monitorized with ECG, pulse oximetry (SpO2), and non-invasive arterial pressure (NIAP). After the first arterial pressure was measured, patients were premedicated with intravenous (IV) fentanyl (0.5 µg/kg) and IV midazolam (0.05 µg/kg). Five minutes later second NIAP measures were taken and additional dose of fentanyl (0.5 µg/kg) was given. After DSA again 5 mL of blood samples were taken twice to the two tubes with EDTA (from group II only).

Immunofluorescent painting (NK numbers)

NK (CD56) cells were marked by specific antibodies (CD3 FITC, CD16+56+ PE ve Perforin expression FITC) which were marked with fluorescein isothiocyanate (FITC) or phycoerythrin (PE). For FITC 530 nm and for PE/PI, 585 nm emission wavelengths were used and for the reflection 488 nm wavelengths were used. For every sample 10.000 cells were counted and the data was analyzed by using FACS Calibur instrument (Becton Dickinson) using CellQuest software in this study. IL-1β, IL-2, IL-4, IL-10, IL-12, TNF-α, and IFN-γ cytokine levels were measured.

SSC/FSC cartography mapping method was used for flow cytometric research and following immune cells were identified: CD3, CD4, CD8, CD19, CD25, CD40, CD56, CD16+56+.

Multiple analyte platform (XMAP, Luminex)

Twenty-five µl of standards and samples were pipette and incubated on the plate shaker with at 500 RPM in room temperature for 30 minutes. After plate contents were vacuumed 150 µl of washing solution and 25 µl of detection antibody were added and incubated on the plate shaker at 500 RPM in room temperature for 30 minutes. Every sample was washed three times and again 50 µl of streptavidin-PE was added and incubated at 500 RPM in room temperature for 30 minutes. Then washing procedure was performed again. 120 µl of reading buffer was added and on the plate shaker they were incubated for 5 minutes. The data then was read on multiple analyte platform (Luminex).

Statistical Analysis

All data collected from each patient 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

Statistical analysis showed no difference between the two groups in terms of demographic variables and basic physiological measures (data not shown). Cytokine levels in patients who did not receive analgesia-sedation showed a trend to increase in the majority of the molecules after the procedure except IL-1β which was significantly higher before the procedure (paired sample t test; $p = 0.00001$). TNF-α showed a small increase after cerebral DSA but the difference was not statistically significant (paired sample t test; $p = 0.29$). Table I summarizes the measures regarding the cytokines in patients who did not receive analgesia-sedation before and after cerebral DSA. In contrast to group I, in group II including patients who received analgesia-sedation before and after cerebral DSA, cytokine levels showed variable trend. IL-10, IL-12 and IFN-γ increased and the rest decreased significantly (paired sample t test; $p < 0.05$) (Table II). When comparing the two groups regarding cytokine levels after cerebral DSA, statistical analysis showed that IL-1β, IL-10, IL-12, and IFN-γ levels increased significantly (independent sample t test; $p < 0.05$) in analgesia-sedation group. On the other hand analgesia-sedation caused significant decrease in IL-2, IL-4, and TNF-α levels in the same group (independent sample t test; $p < 0.05$). Table III shows the summary of the data between the two groups.

Regarding lymphocyte levels in the groups before and after cerebral DSA, CD40 (paired sample t test; $p = 0.01$) and CD56 (paired sample t test; $p = 0.004$) levels were significantly higher after the procedure in patients not received analgesia-sedation (Table IV). Patients who received analgesia-sedation (group II) before and after cerebral DSA showed significant increase in CD4, CD19, CD25, CD3, and CD40 levels following DSA (paired sample t test; $p < 0.05$) and other parameters did not show significant difference (paired sample t test; $p > 0.05$). Table V summarizes the comparisons before and after cerebral DSA in group II. Comparing the two groups with respect to lymphocytes after cerebral DSA showed

Table I: A Summary of Statistical Results Showing Comparisons with Respect to Cytokines in Patients (Group I) Who were not Given Analgesia-Sedation before and after Cerebral DSA

Variables (pg/ml)	Before DSA	After DSA	p value
IL-1β	24.03 ± 2.3	16.3 ± 1.0	0.00001
IL-2	26.9 ± 1.8	31.1 ± 2.0	0.00001
IL-4	17.3 ± 2.2	31.5 ± 2.2	0.00001
IL-10	30.9 ± 3.1	33.9 ± 2.8	0.00001
IL-12	17.4 ± 1.3	18.9 ± 1.4	0.002
TNF-α	24.2 ± 1.6	25.3 ± 1.3	0.29
IFN-γ	24.3 ± 2.2	35.3 ± 2.4	0.00001

DSA: *Digital subtraction angiography.*

Table II: A Summary of Statistical Results Showing Comparisons with Respect to Cytokines in Patients (Group II) Who Received Analgesia-Sedation before and after Cerebral DSA

Variables (pg/ml)	Before DSA	After DSA	p value
IL-1β	32.7 ± 3.9	24.7 ± 3.8	0.00001
IL-2	34.3 ± 2.3	24.6 ± 1.8	0.00001
IL-4	23.2 ± 2.2	18.7 ± 1.9	0.00001
IL-10	29.7 ± 2.4	41.9 ± 2.3	0.00001
IL-12	21.1 ± 2.3	30.4 ± 5.8	0.00001
TNF-α	19.5 ± 2.4	11.3 ± 2.4	0.00001
IFN-γ	29.1 ± 3.0	42.1 ± 2.6	0.00001

DSA: *Digital subtraction angiography.*

that CD56 (independent sample t test; p = 0.00001) and CD56 (independent sample t test; p = 0.00001) levels were significantly higher in patients received analgesia-sedation and other parameters did not show significant differences (independent sample t test; p < 0.05). Table VI shows the differences between the two groups after DSA regarding lymphocytes. In our study when we compared the levels of immune cells, in Group I (lack of sedation) level of CD40 and CD56 were significantly elevated, where as other immune cells did not differ too much (Table 6).

Table III: A Summary of Statistical Results Showing Comparisons with Respect to Cytokines between the Two Groups after DSA

Variables (pg/ml)	Group I (n = 7)	Group II (n = 34)	p value
IL-1β	16.3 ± 1.0	24.7 ± 3.8	0.00001
IL-2	31.1 ± 2.0	24.6 ± 1.8	0.00001
IL-4	31.5 ± 2.2	18.7 ± 1.9	0.00001
IL-10	33.9 ± 2.8	41.9 ± 2.3	0.00001
IL-12	18.9 ± 1.4	30.4 ± 5.8	0.00001
TNF-α	25.3 ± 1.3	11.3 ± 2.4	0.00001
IFN-γ	35.8 ± 2.4	42.1 ± 2.6	0.00001

DSA: *Digital subtraction angiography.*

Table IV: A Summary of Statistical Results Showing Comparisons with Respect to Lymphocytes in Patients (Group I) Who were not Given Analgesia-Sedation before and after Cerebral DSA

Variables (pg/ml)	Before DSA	After DSA	p value
CD4	35.5 ± 7.6	33.4 ± 9.3	0.55
CD8	14.1 ± 3.3	16.7 ± 3.0	0.27
CD19	6.39 ± 3.0	6.9 ± 2.2	0.56
CD25	4.15 ± 1.6	3.25 ± 0.7	0.19
CD3	53.09 ± 10.2	57.3 ± 11.6	0.55
CD16+56+	31.4 ± 6.6	30.7 ± 4.8	0.76
CD56	12.7 ± 3.7	22.1 ± 4.3	0.004
CD40	3.93 ± 1.8	7.46 ± 2.0	0.01

DSA: *Digital subtraction angiography.*

Table V: A Summary of Statistical Results Showing Comparisons with Respect to Lymphocytes in Patients (Group II) Who Received Analgesia-Sedation before and after Cerebral DSA

Variables (pg/ml)	Before DSA	After DSA	p value
CD4	21.4 ± 9.1	32.9 ± 9.9	0.00001
CD8	16.1 ± 7.0	13.8 ± 7.0	0.12
CD19	6.1 ± 2.9	7.8 ± 4.2	0.04
CD25	2.75 ± 1.3	6.2 ± 2.6	0.00001
CD3	46.3 ± 16.8	52.7 ± 16.9	0.05
CD16+56+	29.9 ± 9.7	30.4 ± 11.4	0.78
CD56	10.5 ± 4.2	12.2 ± 4.0	0.11
CD40	3.9 ± 1.9	6.11 ± 3.1	0.001

DSA: *Digital subtraction angiography.*

Table VI: A Summary of Statistical Results Showing Comparisons with Respect to Lymphocytes Between the Two Groups after DSA

Variables (pg/ml)	Group I (n = 7)	Group II (n = 34)	p value
CD4	33.4 ± 9.3	32.9 ± 9.9	0.90
CD8	16.7 ± 3.0	13.8 ± 7.0	0.29
CD19	6.9 ± 2.2	7.8 ± 4.2	0.40
CD25	3.25 ± 0.7	6.2 ± 2.6	0.00001
CD3	57.3 ± 11.6	52.7 ± 16.9	0.50
CD16+56+	30.7 ± 4.8	30.4 ± 11.4	0.92
CD56	22.1 ± 4.3	12.2 ± 4.0	0.00001
CD40	7.46 ± 2.0	6.11 ± 3.1	0.28

DSA: *Digital subtraction angiography.*

DISCUSSION

Inflammation plays a central role in cases in which any harm to the tissues occurs. The inflammatory processes include a cascade of events that cause several systems such as neurovascular and humoral/cellular immune systems to act together in order to make a response and repair damaged tissues (1, 5, 13). It has been demonstrated that in the inflammation several endogenous and exogenous stimulations by several molecules including cytokines and lymphocytes lead to activate complex defense systems in vascularized tissues in which blood vessels are found in the center of the reactions. However; it should be noted that chains of reactions for the defense of the organism may also cause tissue traumas (4, 13) but repair mechanisms are activated and try to oppose the detrimental effects of inflammation.

Cerebral DSA is invaluable tool in diagnosis and treatment of certain intracranial and extracranial vascular pathologies and use of cerebral DSA has been dramatically increased and continues to increase year by year. Since it is a common and invasive intervention, occurrence of inflammation is inevitable and the rationale behind this study is to bring attention of the clinicians who are involved in the procedure, to the inflammatory reactions that may lead to detrimental complications if not prevented. This is the first report aiming to focus on the major cytokines and lymphocytes following cerebral DSA in the current literature.

Surgical stress activates several pro-inflammatory molecules such as IL-1, and TNF-α secreted by monocytes, macrophages and lymphocytes which in turn activate hypothalamus-hypophysis-adrenal axis (HHA) (3). Hence, neuroendocrine system and pro- and anti-inflammatory cytokines synergistically increase their suppressive effects on the immune system. The immunosuppressive effect that is predominated before surgery due to active neuroendocrine and hypercytokinemia may negatively influence clinical course of the patients after surgery (16).

The current study showed significant differences between before and after cerebral DSA regarding the cytokines except TNF-α in patients who did not receive analgesia-sedation. IL-1β levels decreased after the procedure while IL-2, IL-4, IL-10, IL-12, and IFN-γ increased compared to the levels before cerebral DSA. Comparing immune cells in this group of patients showed significant increase after cerebral DSA in CD40 and CD56 levels and changes in other cells did not reach significant level. We determined that although TNF-α, which plays an active role in stimulation of phagocyte by macrophages and of anti-inflammatory cytokines (IL-4, IL-10, IL-13) and in maintaining the balance among the cytokines, did not show change, anti-inflammatory cytokines increased after cerebral DSA in patient without analgesia-sedation. It has been known that TNF-α together with IL-1β provide activation of helper "T" [(Th) CD4] cells which secrete IL2. Upon secretion, IL-2 by paracrine and autocrine actions leads to increase in the levels of IL-2 and IFN-γ receptor expressions which in turn increase CD56 stimulation. IL-1β and TNF-α play a role in the formation of both humoral and cellular immunity. Depending on our results we can speculate that decrease in IL-1β, CD4 and steady state in TNF-α may be a triggering factor for the suppression of both humoral and cellular responses in patients without analgesia-sedation. The suppression of the immunity may further be due to the opposite effects of other cytokines on IL-1β and TNF-α (14).

The data led us to conclude that in patients without analgesia-sedation in our study the activity of IL-2 has increased because of its level has increased although CD4 levels did not change. IL-2 activates CD4 (growth factor), CD8, and CD56 and CD19, and triggers antibody production from CD19. Moreover IL-2 also increases cytolytic functions by activating CD56. It could be possible that the activations of cytotoxic cells and all the cells bearing interleukin-2 receptors (IL-2R or CD25) such as CD8, CD19, CD56 etc. are kept in certain limits since our results showed that CD25 (IL-2R) levels did not change significantly in patients who did not receive analgesia-sedation. IL-4 stimulates the development of Th2 cells from CD4. IFN-γ suppresses cell-mediated immunity by antagonizing the action of macrophage activating factor (MAF). However; IL-10 produced mainly from CD19 and neutrophils is capable of inhibiting synthesis of pro-inflammatory cytokines such as IL-1β, TNF-α, IFN-γ, IL-6, and IL-8 (14). Our findings are in

line with the current literature regarding the cytokines except IFN-γ which showed increased level. Increase in CD40 levels on CD19 molecules might have been due to stimulation of CD19 to produce CD40 by increased IL-4 level although CD19 (B lymphocyte) levels did not change. IL-4 reacts with CD40L on the active T cells and induces antibody production from CD19 (B lymphocyte) cells. Severe immune deficiency has been demonstrated in the absence of CD40 and CD40L molecules in previous studies (10, 17).

In patients without analgesia-sedation, our results have demonstrated that significant increase in either pro-inflammatory as IL-2 and IFN-γ or anti-inflammatory cytokines (such as IL-4 and IL-10) could be explained by the balancing effects of regulatory molecule IL-12 makes us to think that there may be a coherent relationship between balancing effects of IL-2 and the actions of Th1/Th2 cytokines.

In patients who received analgesia-sedation, all measures taken before and after cerebral DSA showed significant changes. While IL-1β, IL-2, IL-4, and TNF-α decreased, IFN-γ, IL-10, and IL-12 have increased after cerebral DSA. Comparing the immune cells before and after cerebral DSA, CD4, CD3, CD19, CD25, and CD40 levels were significantly higher after the procedure. We found that analgesia-sedation suppresses pro-inflammatory cytokines except IFN-γ and increase anti-inflammatory cytokines except IL-4 and regulatory acting IL-12. Although IL-1β and TNF-α decreased after cerebral DSA, significant increase in CD3, CD4, CD19, CD25, and CD40 levels were found. It is demonstrated that IL-2 and IFN-γ act as a suppressor molecule for Th2 cytokines. Although IL-2 decreased, CD25 (IL-2R) increased significantly. This might be due to increased number of cells harboring these receptors (IL-2R). The increase levels of CD4, IFN-γ and IL-12 and unchanged CD56 levels might result from the effects of decreased IL-2 levels. CD40, a T cell activator and surface receptor of CD19, has increased parallel to CD19 (B lymphocyte) incline.

In patients who received analgesia-sedation comparing measures before and after cerebral DSA demonstrated that premedication has suppressed pro-inflammatory cytokines while stimulated anti-inflammatory cytokines together with humoral and cellular immune cells. With this respect, we conclude that following activation of non-specific immune system, stronger defense mechanism which is specific immune system is strongly activated.

Given that the main object of our study is to compare measures taken after cerebral DSA between patients who did not receive and those who did receive analgesia-sedation, the two groups showed significant differences regarding all molecules studied. IL-10, IL-12 and IFN-γ values were found to be higher but IL-1β, IL2, and TNF-α decreased in case of analgesia-sedation application. Comparing immune cells showed significant difference between the groups with respect to CD56 and CD25 (IL-2R) which is concordant with the literature (2, 6, 8, 18).

Decreased IL-2 due to analgesia-sedation shows its effect by increased CD25 (IL-2R). On the other hand, CD6 that bears IL-2Rs on its surface significantly decreased even though increase in IL-12 and IFN-γ levels. In the current study analgesia-sedation has led to suppression of some pro-inflammatory cytokines (IL-2 and TNF-α) and to increase some pro-inflammatory cytokines (IL-1β and IFN-γ) together with some anti-inflammatory cytokines (IL-10 and IL-12). However; the precursor defense cell, CD56 (NK-natural killer) and specific immune system cells such as CD4, CD8, CD19 and CD3 on which the cytokines, just mentioned above, have direct effects, did not show significant changes. These results suggest that analgesia-sedation stimulates the immune system by way of cytokine cascade in order to trigger defense mechanism(s) (2, 6, 8, 18).

CONCLUSION

This study tried to figure out the influence of analgesia-sedation on the immune system following an invasive stressful intervention, here cerebral digital subtraction angiography. Results suggest that analgesic and sedative agents may play an important role on the secretion of different pro- and anti-inflammatory cytokines and lymphocytes following an invasive procedure. So that features, types, duration of use during the procedure, dosages of the analgesics and sedative agents may help to predict what type(s) of cytokines will be secreted. Because different types of cytokines secreted from different type of cells can either act on different or the same targets. Depending on the current results, it can be speculated and be possible that delimitation of the action(s) of the cytokines affecting the secretion or activation of CD56 (NK) may avoid complications of inflammation after invasive procedures. However; this possibility warrants further prospective clinical studies including larger population of patients.

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