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The Effects of Three Neurosurgical Anaesthetic Methods on HLA-Dr Expression

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Abstract: Expression of human leukocyte antigen-DR (HLA-DR) is considered a meaningful indicator of immune response because of the important role that HLA-DR plays in presenting antigen to T-lymphocytes. The aim of this study was to evaluate the effects of three anaesthetic methods (intravenous anaesthesia with propofol-fentanyl and balanced anaesthesia with isoflurane-fentanyl or sevoflurane-fentanyl) on monocytic HLA-DR expression in neurosurgical patients who underwent craniotomy. Thirty patients were divided into 3 groups of 10, and each group was the subject of one of the anaesthetic regimes noted above during craniotomy procedures. Blood samples were collected and HLA-DR expression was measured by flow cytometry at 15 minutes before induction, 1 hour into surgery, 3 hours after surgery, and on postoperative day 3. Comparing the levels of expression at each given stage between and within groups, there were no significant differences found at any time point except on the third postoperative day. For all groups, HLA-DR expression on postoperative day 3 was significantly higher than that measured in the first three stages (p<0.05). The results indicate that neither intravenous anaesthesia nor balanced anaesthesia has any significant effect on monocytic HLA-DR expression in neurosurgical patients.

Key Words: Intracranial surgery, Immune response, Anaesthetic agents, Immunosuppression, HLA-DR

Introduction

Despite the advances that have been made in operative technique and in perioperative and postoperative management, infection continues to be a major problem in surgical patients. The reported rate of infection in neurosurgical patients after craniotomy is reported to be 9%, a significantly high level that is believed to be linked to a disturbance in immunoreactivity (1,2).

The potential effects of anaesthetic agents on the immune system are a constant focus of attention in the field of anaesthesia. The reason behind the concern is that the risk of postoperative infection and the risk of bone marrow suppression both rise as a result of longer durations of anaesthesia (3). Currently, it is considered that anaesthesia and surgery combine to affect the immune system in various ways, and the effects depend on the different components of both contributors. Perhaps due to the complexities involved, studies on immunity following the combination of anaesthesia and intracranial surgery have yielded conflicting results (4-14). The impairment of neurosurgical patient immunoreactivity after surgery may also be associated with other factors, including systemic illness, the intracranial pathology involved, length of surgery, and anaesthetic management and methods.

The immune system has evolved to protect the individual from a hostile environment containing innumerable viruses, bacteria and other parasites. To do so effectively, the immune system must discriminate "nonself" from "self." This crucial discrimination is achieved via the molecules of the major histocompatibility complex (MHC). One of the best known MHC molecules in humans is the human leukocyte antigen (HLA). HLA molecules, and the genes that encode them, fall into three categories: classes I, II, and III. Class II molecules include HLA-DR, -DQ, and –DP molecules. HLA class II molecules are found chiefly on immunocompetent cells, B lymphocytes, antigen-presenting cells, and activated T cells in humans. The function of class II molecules is to present processed antigenic peptide fragments to CD4 T lymphocytes during the initiation of immune responses (15).

Monocytes and macrophages express class II MHC antigens (HLA-DR, -DP, and –DQ), gamma interferon receptor, aminopeptidase N (CD13), receptors for complement components, and receptors for Fc region of IgG. Mature monocytes express high levels of a relatively monocyte-specific antigen, CD14. Monocyte and macrophage development is affected by the secretion of cytokines, lymphokines and interferons by activated T lymphocytes (16).

Expression of HLA-DR is considered a meaningful indicator of immune response because of the important role that HLA-DR plays in presenting antigen to T-lymphocytes (17). Inflammation is the human organism's general response to trauma. The clinical picture of this response is variable, and is influenced by many factors. In patients who have been exposed to major trauma, it appears that the systemic inflammatory response is followed by monocyte deactivation. This deactivation is characterized by a decrease in monocytic HLA-DR expression, which indicates severe immunosuppression and high risk of infection (18,19).

Although it is not realistic to isolate anaesthesia from surgery, different anaesthetic methods may have different impacts on the immune response of patients with similar intracranial pathology who undergo similar surgery. Our aim in this study was to use this approach to assess the effects of three separate anaesthetic agents based on levels of monocytic HLA-DR expression.

Materials and Methods

The study group consisted of 30 adult female American Society of Anaesthesiologists class I and class II patients who were admitted to Çukurova University Hospital for elective craniotomy as treatment for intracranial space-occupying lesions. Twenty-three of the women had intracranial masses, five had cerebral aneurysms and two had arteriovenous malformations. None of the patients had any immunologic pathology or infection. The patients were equally divided into three groups, and we followed a different anaesthetic protocol for each group.

Our intent was to avoid confounding factors that might affect immune response. We studied only those patients scheduled for craniotomy. All patients received the same amount of transfused blood, as well as the same dosages and types of drugs. Each individual was premedicated with midazolam (0.6 mg kg^{-1} intravenously [i.v.]) 10 minutes before the operation, at which time we also collected a preoperative blood sample. We monitored vital signs using EKG (Petaş KMA 250), a noninvasive blood pressure monitor (Criticare Systems INC 1100), a pulse oxymeter (Ohmeda RGM 5200) and a capnograph (Criticare Systems INC 1100).

All patients were initially given 100% O_2 by mask for 5 minutes, and then underwent anaesthetic induction with an i.v. mixture of fentanyl (1.5 µg kg^{-1}) and propofol (1%, 2.5-3.0 mg kg^{-1}). When the eyelash reflex could no longer be elicited, we started assist-ventilation with 100% O_2, and then administered succinylcholine (1.5 mg kg-1 i.v.) and 2% lidocaine (1.5 mg kg^{-1} i.v.). Once the neuromuscular blockade was sufficient, we intubated the patient with a spiralled endotracheal tube. The blockade was maintained using vecuronium (an initial dose of 0.1 mg kg^{-1} followed by increments of 0.025 mg kg^{-1} every 30 minutes). Controlled ventilation was continued, with end-tidal pressures that held CO_2 levels at 25-27 mmHg. We also placed a cannula in the radial artery for invasive blood pressure monitoring (Hewlett-Packard 78353-B), and a central venous cannula in the right internal jugular vein for monitoring central venous pressure (CVP) (Hewlett-Packard 78353-B). A Foley catheter was inserted to follow urine output.

After induction, each patient was started on the assigned maintenance anaesthetic protocol. Group 1 individuals (n=10) received intravenous anaesthesia (IVA) (infusion of 4-5 mg kg^{-1} min^{-1} propofol [1%] plus 3 µg kg^{-1} min-1 fentanyl). Group 2 (n=10) received 0.5-1 minimum alveolar anaesthetic concentration (MAC) isoflurane and 100 µg i.v. fentanyl every 30 minutes. Group 3 (n=10) received 0.5-1 MAC sevoflurane and 100 µg i.v. fentanyl every 30 minutes.

Fifteen minutes before opening the dura mater, we administered 1 mg kg^{-1} of 20% mannitol and 16 mg dexamethasone i.v. During the operation, we adjusted the concentrations of all three anaesthetics within the limits listed above in order to maintain CVP at 6-8 mmHg and mean arterial pressure (MAP) at 50-70 mmHg before the mass was removed or the aneurysm was clipped. The targets for after the procedure were 8-10 mmHg and 70-100 mmHg, respectively. Each patient in the study required one unit of whole blood. We assist-ventilated the patients during the suturing of the subcutaneous tissue, then reversed the neuromuscular blockade with i.v.

injections of atropine sulphate (0.015 mg kg^{-1}) and neostigmine methylsulphate (0.5 mg kg^{-1}), and extubated the patient.

All patients received 1 g ceftriaxone and 500 mg amikacin daily for the first 5 days of the postoperative period, and for the first 3 days were given dexamethasone (4x8 mg i.v.) and 20% mannitol (1 mg kg^{-1} i.v.) as well. Each individual was followed for 10 days postoperatively. Patients were defined as having infectious complications if they exhibited a clinically evident systemic response to infection and clinical evidence of an infection site.

We determined monocytic HLA-DR values in blood samples collected at the following four times: 15 minutes before induction (stage I), 1 hour after induction (stage II), 3 hours postoperatively (stage III), and on postoperative day 3 (stage IV). For the determination of HLA-DR positive monocytes, venous blood samples were involved in a reaction with specific fluorescein isothiocyanate-conjugated anti-HLA-DR monoclonal antibodies (CD14-FITC, Coulter, lot no: 701204 and CD11b-FITC, Coulter, lot no: 729012). By using a flow cytometry apparatus (Epics XL-MCL Coulter) the area of monocytic population was gated and the degree of fluorescence was expressed as a percentage of positive cells. The detailed method was as follows:

We added a 1 ml sample of venous blood to an EDTA tube. From this sample, a 100 µl aliquot was transferred to a 12x75 mm tube and then mixed with 10 µl of FITC antibodies. The mixture was incubated at room temperature for 10 minutes. Then it was transferred to a Q-prep apparatus (Coulter-USA-6704203) and the following solutions were added, in order: 600 ml Immunoprep A (1.2 ml L^{-1} formate) for red blood cell lysis, 265 ml of Immunoprep B (6 g L^{-1} sodium carbonate, 14.5 g L^{-1} sodium chloride, 31.3 g L^{-1} sodium sulphate) for leukocyte stabilization, and 100 ml of Immunoprep C (10 g L^{-1} formaldehyde, 14 ml L^{-1} buffer) for membrane stabilization. Following these additions, the tubes were incubated in the dark for 20 minutes at room temperature. Then, by using the flow cytometry apparatus (XL-Coulter- USA), the percentage of HLA-DR positive cells was determined.

Statistical analysis involved the Mann Whitney U and Wilcoxon tests, and was carried out using the software SPSS for Windows. P values<0.05 were considered to indicate significance.

Results

The three groups (IVA, isoflurane, and sevoflurane) were similar with regard to patient age and duration of surgery (p>0.05) (Table 1). A comparison of HLA-DR values in the groups at different stages (I, II, III, and IV) revealed no significant differences between the groups. However, within each group, the HLA-DR values in the first three stages were statistically similar, but the values on postoperative day 3 (period IV) were significantly higher (p<0.05) (Table 2). None of the patients developed infectious complications postoperatively.

Discussion

Currently, we know that postoperative immunologic changes depend mostly on a patient's primary pathology and the associated surgical management (3,6,12,14). Many clinical and experimental studies have documented immunologic changes after trauma or haemorrhage. It is believed that anaesthesia, neuroendocrine response, blood or plasma transfusions, and certain types of surgery may impair patient immune response (3,6,11,12,14,20-26).

As mentioned, the specific interaction between anaesthetics and immunity has been the focus of much research. One study reported that a group of patients who received thiopental/fentanyl induction and isoflurane/nitrous oxide (N$_2$O) maintenance anaesthesia

	Group 1 (IVA)	Group 2 (Isoflurane)	Group 3 (Sevoflurane)
AGE (years)	45.80 ± 12.48	47.80 ± 19.19	40.40 ± 16.03
DURATION OF SURGERY (hours)	3.6 ± 0.84	4.35 ± 1.29	4.55 ± 2.50

Table 1. Patient age and duration of surgery for the three anaesthetic groups.

Abbreviations: IVA; Intravenous anaesthesia

Table 2. The groups' HLA-DR levels (%) at the four different stages.

Stage	Group 1 (IVA)	Group 2 (Isoflurane)	Group 3 (Sevoflurane)
I	28.74 ± 17.47	33.82 ± 7.09	31.28 ± 15.17
II	39.07 ± 15.96	37.65 ± 8.90	44.07 ± 13.95
III	38.71 ± 16.94	42.31 ± 14.27	40.59 ± 17.62
IV	46.52 ± 17.62[A]	50.35 ± 5.79[B]	45.68 ± 11.89[C]

Abbreviations: IVA; Intravenous anaesthesia

[A, B, C]: In each group, the HLA-DR level at stage IV was significantly higher than the levels in the first three stages ($p<0.05$).

exhibited signs of depressed immunity even before their surgery began (21). Many reports on the immune effects of anaesthetic agents, and particularly investigations that have not involved surgical stimulus, have shown that anaesthetics cause dose-dependent inhibition of neutrophil, monocyte and lymphocyte activity (3,27).

Stevenson et al. (11) designed a system to deliver inhalant anaesthetics to leukocyte cultures in vitro, and determined that the viability of monocytes and lymphocytes was not impaired after 4 hours of exposure to halothane, or at the end of the 48-hour culture period. However, 4 hours of exposure to halothane in vitro substantially depressed the release of gamma-interferon from lymphocytes and alpha-interferon from monocytes, particularly at higher halothane concentrations. Clearly, monocytes were more responsive to the immunosuppressive effect of halothane than were lymphocytes. Other reports have supported these findings and some studies have also demonstrated that halothane interferes with monocyte chemotaxis (28).

Most of the specific cellular immunity studies done on T-lymphocytes in vitro have shown a decrease in the T-lymphocyte response to mitogen stimulation (11,29-31). Other in vitro studies have revealed no change in T-lymphocyte function under these conditions (32,33). In vivo investigations of T-lymphocyte function have shown that the combination of anaesthesia and surgery decreases both the proliferation response and the number of circulating T-cells (6,8,11,33-35). However, testing done in volunteers who were not subjected to a surgical stimulus indicated that halothane and enflurane cause no significant changes in the number or function of T-cells. Reports have also shown no measurable impairment of T-

lymphocyte immune function in operating room personnel who have been chronically exposed to such gases (12,24,36-38).

Regarding the immunity-related effect of surgery itself, investigations have revealed no detectable change in the immune response in cases of minor surgery, but have found immune system imbalances associated with major surgical trauma (12,24,33). Interestingly, in terms of combined effects, research has also shown that regional anaesthesia may alter T-lymphocyte response following major surgery (24,39).

As mentioned earlier, HLA-DR is important in antigen presentation and the development of the antigen-specific T-cell response. A number of researchers have documented an association between decreased HLA-DR expression and the functional deactivation of monocytes, and have stated that decreased HLA-DR expression may be a sign of severe immunosuppression (18,20). Asadullah et al. (20) detected a decrease in monocytic HLA-DR expression after intracranial surgery, and reported that patients with low HLA-DR expression tended to develop more infectious complications.

There are many possible factors that can affect the monocytic HLA-DR expression like local inflammatory response, cytokines (IL-10, transforming growth factor-β, δ-interferon), blood transfusion, corticosteroids and others.

The brain is the source of many classic mediators of inflammation (40-42). Some central nervous system tumours have the capacity for cytokine production (43,44). The neuroendocrine axis is a regulatory system controlling systemic inflammatory responses and the macrophage migration inhibitory factor is a pituitary-derived cytokine (45). On the other hand, there is a hypothesis that the local inflammatory response in the central nervous system shortly after trauma is followed by an anti-inflammatory response that becomes systemic also. Possibly involved in this anti-inflammatory response are the immunosuppressive cytokines, IL-10 and transforming growth factor-b, which reduce monocytic HLA-DR expression in vitro (46,47). Another point is that monocyte and macrophage development is affected by the secretion of cytokines, lymphokines and interferons by activated T lymphocytes. For example, d-interferon produced by activated T cells stimulates and increases the amount of MHC glycoproteins on monocytes and macrophages, allowing for more efficient antigen

presentation (16). Schmand et al. (48) showed that haemorrhage alone can induce the suppression of macrophage function in animals. However, in another trial (49), there was no difference in monocytic HLA-DR expression between high and low blood transfusion groups. It is also known that corticosteroids can down-regulate the monocytic HLA-DR expression and suppress the hypothalamic-pituitary axis. All or some of the factors above might contribute to levels of HLA-DR expression.

We did not detect the local anti-inflammatory response since we did not measure the cytokine levels in the serebrospinal fluid. However, we did not observe any systemic anti-inflammatory response either. So even if there had been a local response, it did not become systemic or clinically detectable.

In our study, we limited the blood transfusion volume by one pack and all of our patients received the same application of dexamethasone in the perioperative and postoperative period. In other words, all patients were in the same condition regarding blood transfusion and steroid therapy.

We can not exclude the possibility that monocytic HLA-DR expression might have been influenced by some or all the factors listed above; however, we did not detect any adverse effect of these factors that were clinically relevant.

Actually, preoperative monocytic HLA-DR values were our control values in a way because at that period interval there was no anaesthetic or surgical trauma to the patients so we accepted that time as immunologically normal. In our study, the monocytic HLA-DR values for the three patient groups before, during, and after surgery remained comparable and unchanged through all stages tested, except for postoperative day 3. So we can speculate that if the decrease in the monocytic HLA-DR expression is a sign of immunosuppression that may be a result of infectious complications, since we did not observe a decrease in the first stage and also between the groups within the stages, there was no immunosuppressive condition. The nonoccurrence of infectious complications also supported our speculation. In contrast to the findings of Asadullah et al., each of our groups exhibited significantly higher monocytic HLA-DR expression on the third day postsurgery compared to the levels recorded in the first three stages ($p<0.05$). The increase in monocytic HLA-DR expression on postoperative day 3 may indicate an improvement in the immune status.

In conclusion, in terms of the importance of anaesthetic choices, our findings indicate that neither IVA nor balanced anesthesia with isoflurane or sevoflurane significantly affected immune responses as reflected by monocytic HLA-DR expression.

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