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Effect of different anesthesia techniques on the serum brain-derived neurotrophic factor (BDNF) levels

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Abstract. – OBJECTIVE: Serum Brain-Derived Neurotrophic Factor (BDNF) levels are associated with neurotransmission and cognitive functions. The goal of this study was to examine the effect of general anesthesia on BDNF levels. It was also to reveal whether this effect had a relationship with the surgical stress response or not.

PATIENTS AND METHODS: The study included 50 male patients, age 20-40, who were scheduled to have inguinoscrotal surgery, and who were in the ASA I-II risk group. The patients were divided into two groups according to the anesthesia techniques used: general (GA) and spinal (SA). In order to measure serum BDNF, cortisol, insulin and glucose levels, blood samples were taken at four different times: before and after anesthesia, end of the surgery, and before transferal from the recovery room.

RESULTS: Serum BDNF levels were significantly low ($p < 0.01$), cortisol and glucose levels were higher ($p < 0.05$ and $p < 0.01$) in Group GA compared with Group SA. No significant difference was detected between the groups in terms of serum insulin levels. There was no correlation between serum BDNF and the stress hormones.

CONCLUSIONS: Our findings suggested that general anesthetics had an effect on serum BDNF levels independent of the stress response. In future, BDNF could be used as biochemical parameters of anesthesia levels, but studies with a greater scope should be carried out to present the relationship between anesthesia and neurotrophins.

Key Words:
BDNF, General anesthesia, Spinal anesthesia, Stress response.

Introduction

Serum Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin which has important effects on neurons in both the central and the peripheral nervous systems and on the growth and differentiation of new neurons and synapses[1,2]. It is active in the regions of the brain such as hippocampus, cortex, cerebellum and basal forebrain where vital functions such as learning, memory and thinking occur[3]. It are increased excitatory neurotransmission with both its presynaptic and postsynaptic effects. BDNF also modulates excitatory and inhibitor synaptic transmission by inhibiting GABA-A receptor meditated postsynaptic current resulting in decreased GABA neurotransmission in the mature brain[4,5]. Brain BDNF expression is decreased with cognitive dysfunction, distorted memory performance, depression, stress and corticosterone exposure[6-8]. BDNF is increased with glutamate, which is an excitatory neurotransmitter, exercise, intellectual stimulation and some medications used to treat depression[8-10].

BDNF is related to synaptic communication in the central nervous system and affected by neurodegenerative diseases and psychiatric problems such as depression. Its expression may change under stress or in the presence of stress hormones. Anesthesia and surgery are factors that increase the stress response[11]. It has been suggested that BDNF could also be affected by surgical and anesthesia applications. In this study, the effects of different anesthesia techniques on serum BDNF levels were investigated. Also, because BDNF may be related to the stress response, it was studied whether the possible BDNF level changes have associated with stress response.

Patients and Methods

After obtaining the approval from Institutional Review Board, oral and written consent were obtained from patients for a prospective randomized

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study. The study included fifty male patients between the ages of 20-40 who were scheduled for inguinoscrotal surgery and who were in ASA I-II risk group. The exclusion criteria were: patients who had psychiatric or endocrine diseases and metabolic syndrome, patients using antidepressants, antipsychotics and steroids and patients who had afternoon operations. This was a prospective randomized study in which patients were split into two groups according to the anesthesia technique: Group GA for general anesthesia (n=25) and Group SA for spinal anesthesia (n=25). The patients who did not have premedication were monitored with electrocardiography, noninvasive blood pressure, peripheral oxygen saturation. The patients who did have general anesthesia were monitored with bispectral index (BIS).

In Group GA, anesthesia were induced with 2 mg/kg propofol, 0.1 mg/kg vecuronium and 2 mcg/kg fentanyl. The anesthesia for these patients was maintained to keep BIS in the range of 40-60 with 2-2.5% sevoflurane in 50% O_2-50% N_2O. Respiration was mechanically maintained with $ETCO_2$ adjusted as 30-40 mmHg. Throughout the surgery, fentanyl for analgesia and vecuronium for muscle relaxation were administered as additional doses when needed. In recovery from anesthesia, when needed, 0.04 mg/kg neostigmine and 0.01 mg/kg atropine were administered intravenously in order to eliminate the residual muscle relaxation effect.

In Group SA, patients were placed in a seated position and the lumbar region was cleaned with antiseptic solution. The hyperbaric bupivacaine (10 mg) was administered into the subarachnoid space between L2-3 or L3-4, with a 25 G Quincke type spinal needle.

Blood samples were taken in 4 periods to measure serum BDNF, cortisol, insulin and glucose levels: before anesthesia induction, after anesthesia induction (but immediately before surgical incision), end of the surgery and during transfer from recovery room to the patient's room. After the blood samples were centrifuged in 1500 rpm for 15 min, they were stored in -70°C. Serum BDNF levels were measured by ELISA. Heart rate (HR) and mean arterial pressure (MAP) of patients was recorded in five-minute intervals, immediately before anesthesia induction and after the anesthesia induction.

Statistical Analysis

Statistical Package for Social Sciences 15.0 program (SPSS Inc., Chicago, IL, USA)was used for statistical evaluation and the obtained data are shown as mean ± standard deviation. To compare the groups, physical ASA risk status of patients was evaluated by Mann Whitney U test and other parameters were evaluated by One-Way ANOVA and t test. Repeated measures were evaluated by Paired-Samples t test for intra-group comparison. It was used Pearson test for correlation. $p < 0.05$ was established as significant.

Results

Three patients were excluded from the study because a patient in general anesthesia group developed laryngospasm in the recovery room and two patients requested to be excluded from the study. Also, a patient in spinal anesthesia group was excluded from the study due to the complaint of pain 15 minutes after the start of the operation. There was no significant difference between ages, ASA physical status, and duration of operation between groups (Table I). The baseline (preoperative) blood glucose, insulin and HOMA-IR levels were within the normal range and BMI was between 18.5 and 25.

When the serum BDNF levels were compared between the groups, it was observed that serum BDNF levels had significantly lower in the Group GA compared to Group SA in the periods after anesthesia induction, and before transferring the patient to service from recovery room (respectively, $p < 0.01$ and $p < 0.001$) (Figure 1). Serum BDNF levels were significantly low before transferring the patient to service from recovery room compared to other three periods in the Group GA (respectively, $p = 0.05$, $p < 0.01$ and $p < 0.01$). Increased serum BDNF levels were also observed in the period before the end of surgery compared to after anesthesia induction in the Group GA ($p < 0.05$). There was no significant difference between the serum BDNF levels in the Group SA.

Serum cortisol levels were significantly higher in the Group GA compared to Group SA after

Table I. Demographic data of groups (mean±SD).

	Group GA	Group SA
Age (year)	26.36 ± 7.24	29.83 ± 8.31
ASA	1.13 ± 0.35	1.25 ± 0.44
Operation duration (min)	75.72 ± 20.20	74.12 ± 18.30

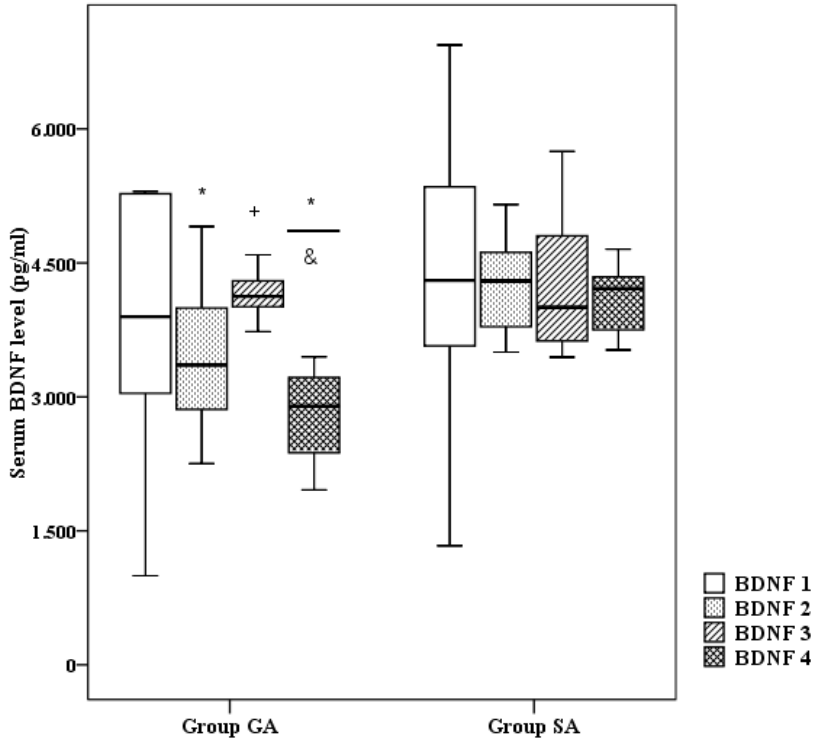

Figure 1. Serum BDNF levels (pg/ml). *: $p < 0.01$, when Group GA compared to Group SA (they were evaluated with One-Way ANOVA and t test) &: $p < 0.05$, when before transferring period was compared to others periods in Group GA (they were evaluated with Paired samples t test).
+: $p < 0.05$, when after anesthesia induction period was compared before the end of surgery in Group GA (they were evaluated with Paired samples t test).

anesthesia induction and before the end of surgery (respectively, $p < 0.05$ and $p < 0.05$) (Figure 2). There was no significant difference in serum cortisol levels between the periods in the Group GA. In Group SA, serum cortisol levels were significantly low before the end of surgery compared to before and after anesthesia induction (respectively, $p < 0.05$ and $p < 0.05$).

There was no significant difference in serum insulin levels between the groups (Figure 3). Serum insulin levels were significantly lower after anesthesia induction than before anesthesia induction ($p < 0.001$) when compared between the periods in the Group GA. At the same time, it was significantly high before transferring from recovery to the service compared to after anesthesia induction and before the end of surgery ($p<0.01$). There was no significant difference in serum insulin levels among the periods in the Group SA.

Serum glucose levels were significantly higher in the group GA than Group SA after anesthesia induction, before the end of surgery and before transferring the patients to the service from the recovery room (respectively, $p < 0.001$, $p < 0.01$ and $p < 0.001$) (Figure 4). In Group GA, we found that serum glucose levels increased in all periods compared to before anesthesia induction (respectively, $p < 0.05$, $p < 0.05$ and $p < 0.001$). The serum glucose levels were significantly higher before anesthesia induction compared to other periods (respectively, $p < 0.001$, $p < 0.01$ and $p < 0.001$). In Group SA, serum glucose levels were significantly higher before transferring from recovery room to the service compared to before to the end of surgery ($p < 0.05$).

When the correlation between serum BDNF levels and stress parameters were evaluated, it was not observed any correlation.

When HR and MAP values were compared between groups, HRs that were measured after 5 and 45 minutes of anesthesia induction and MAPs that were measured at 40th minute were significantly increased in the Group GA compared to Group SA (respectively, $p < 0.01$, $p < 0.05$ and $p < 0.05$). However, we found that HRs

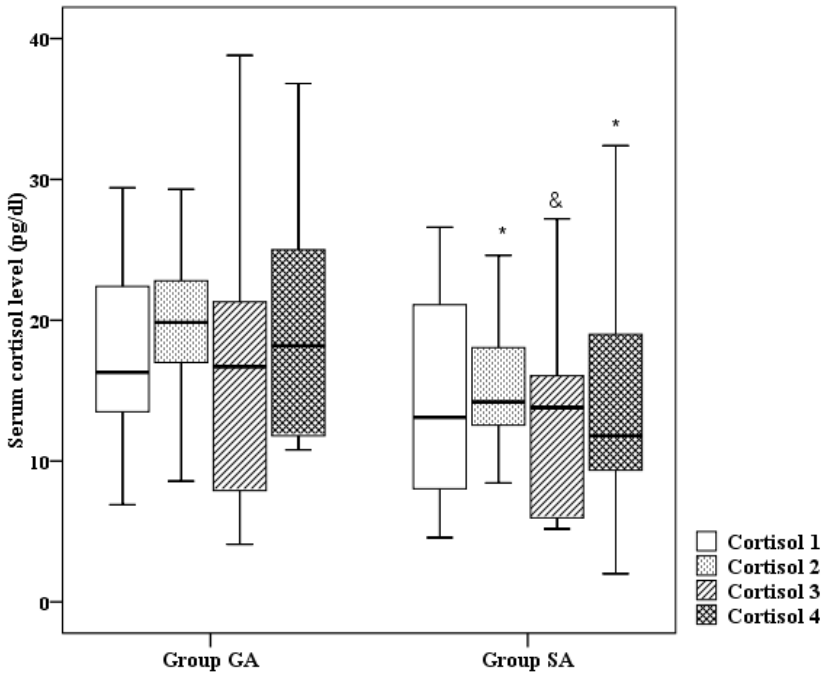

Figure 2. Serum cortisol levels (pg/dl). *: $p < 0.05$, when Group GA compared to Group SA (they were evaluated with One-Way ANOVA and t test); &: $p < 0.05$, when before transferring period was compared to before and after anesthesia induction periods in Group SA (they were evaluated with paired samples *t* test).

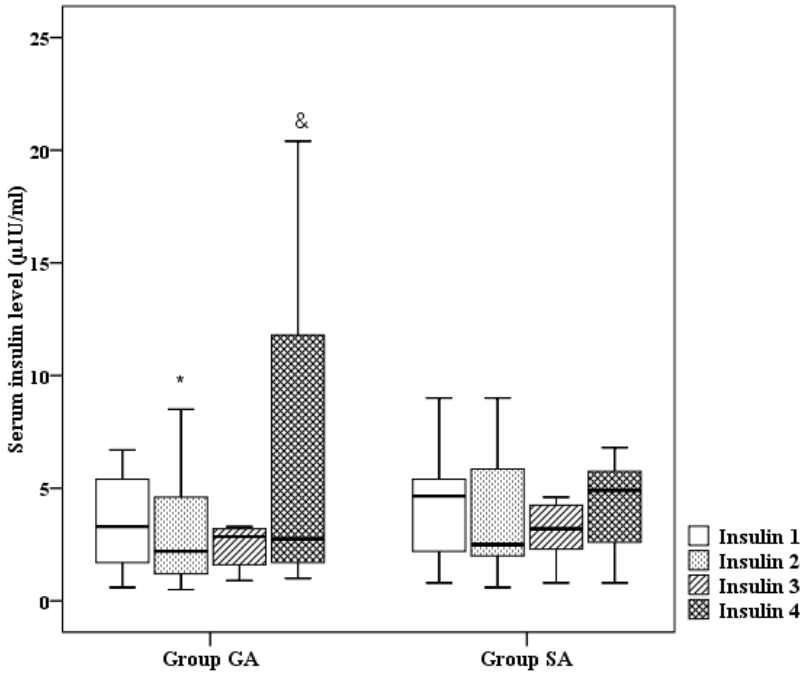

Figure 3. Serum insulin levels (µIU/ml). *: $p < 0.001$, when before compared to after anesthesia induction in Group GA (they were evaluated with One-Way ANOVA and t test) &: $p < 0.01$, when before transferring period was compared to after anesthesia induction and end of surgery in Group GA (they were evaluated with paired samples *t* test).

and MAPs measured at 80th minute were significantly high in the Group SA compared to Group GA (respectively, $p < 0.01$ and $p < 0.05$) (Figures 5 and 6).

Discussion

Our study were assessed the effect of two different anesthesia techniques on serum BDNF, cortisol, insulin and glucose levels and we determined that serum BDNF levels were stable for the patients who received spinal anesthesia. However, in the patients who were applied general anesthesia, serum BDNF levels were decreased by induction, increased towards the end of anesthesia, and were decreased again when the patients fully recovered from anesthesia. Serum BDNF level changes were not related to some stress hormones (cortisol, insulin and glucose).

General anesthetics have depressant effects on central nervous system by changing the inhibitory and/or excitatory neurotransmission[2,3]. BDNF has also effects on presynaptic and postsynaptic transmission and it is stated that BDNF may show these effects as GABAergic beside glutamatergic synaptic transmission[4,5,14]. Low BDNF levels in blood and in cerebrospinal fluid show decline in cognitive function and high BDNF levels show improved cognitive function[15-17]. The patients in the general anesthesia group had fluctuations in serum BDNF levels which can be explained by the depressant effects of general anesthetics especially in cortex and hippocampus which BDNF is intensively in the brain. Since the patients in the spinal anesthesia group do not have central nervous system depression it can be suggested that there is not any fluctuations of BDNF levels.

In a study by Vutskits et al[18] two different general anesthesia techniques were compared for patients having minor surgery; while there was not a significant difference in BDNF level for patients who received thiopental and subsequent isoflurane, it is determined that plasma BDNF levels were decreased after anesthesia induction for patients who received propofol. It has been shown in an experimental study that BDNF protein was decreased in a cortex layer of the brain cortex in patients who received propofol[19]. While BDNF levels are decreased after induction in patients receiving only propofol, this reduction has not been found in patients receiving dexmedetomidine along with propofol[20]. In our study, we found that serum BDNF level was decreased in Group GA

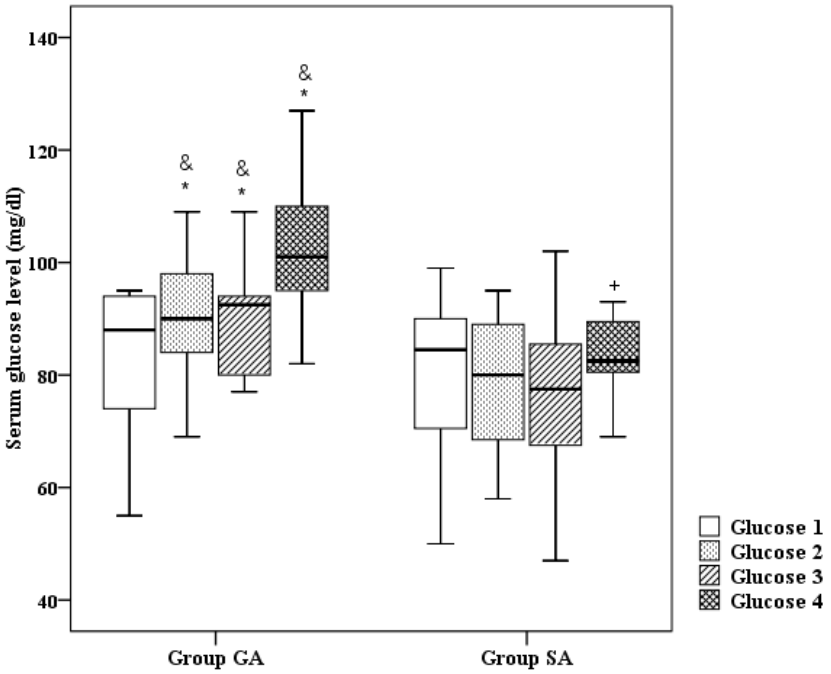

Figure 4. Serum glucose levels. *: $p < 0.01$, when Group GA compared to Group SA (they were evaluated with One-Way ANOVA and t test); &: $p < 0.05$, when before induction period was compared to others periods in Group GA (they were evaluated with Paired samples t test). +: $p < 0.05$, when before transferring period was compared before the end of surgery in Group GA (they were evaluated with Paired samples *t* test).

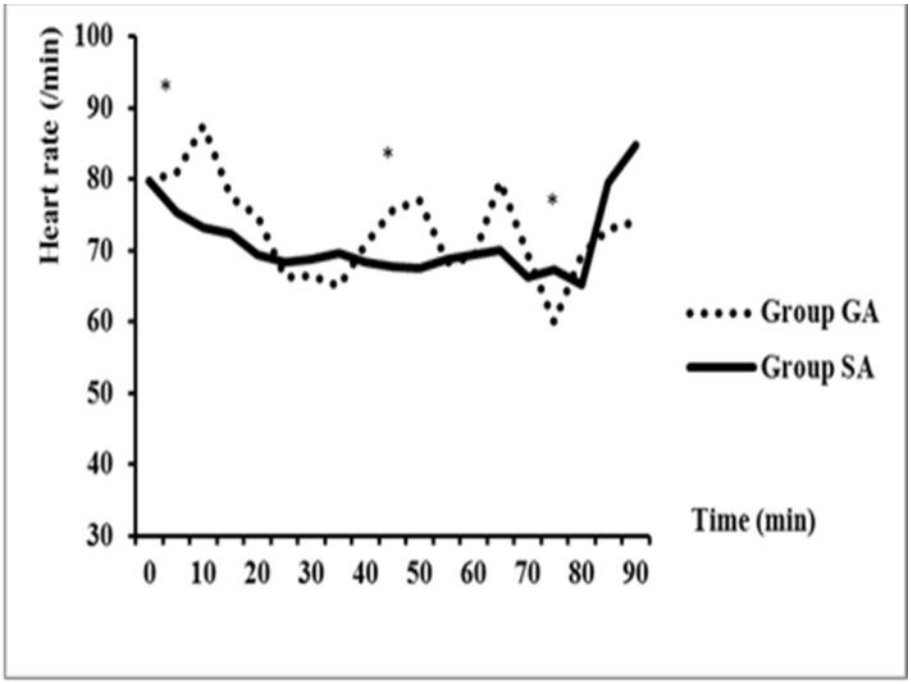

Figure 5. Heart rate of groups (beat/minute). *: $p < 0.05$, when Group GA compared to Group SA at 5th, 45th and 80th minutes (they were evaluated with One-Way ANOVA and t test).

that received propofol for induction. In the same study[19] it was found that isoflurane did not change the BDNF level. In our study, before the end of surgery, BDNF levels were observed to be close to the baseline levels. This status may result from the termination of the effect of propofol and sevoflurane not changed the BDNF levels such as isoflurane. In the same study, Vutskits et al[18] specified that serum BDNF levels were under the basal value at 24 hours postoperative time. In our study, we found that serum BDNF levels that were measured from recovery to transfer to hospital service were under the basal value. BDNF levels were thought to increase during the late period.

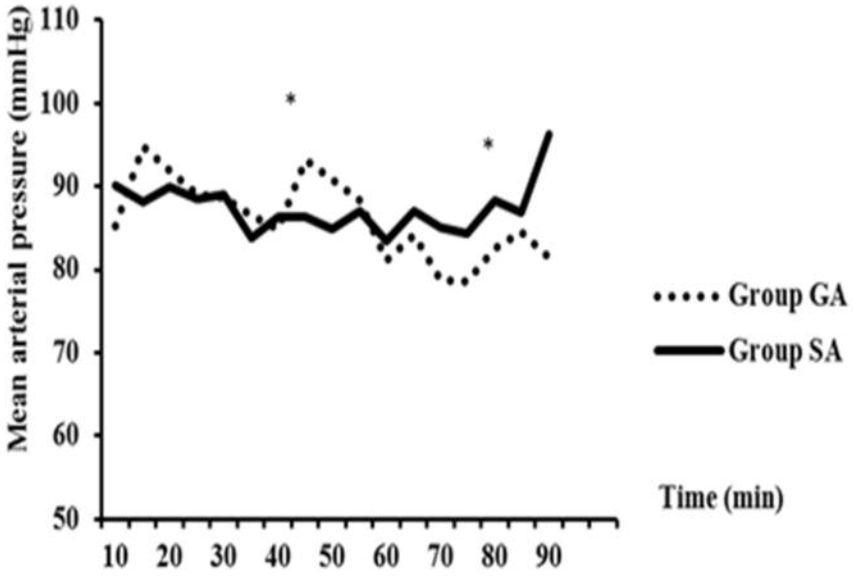

Figure 6. Mean arterial pressure of groups (mmHg). *: $p < 0.05$, when Group GA compared to Group SA at 40th and 80th minutes (they were evaluated with One-Way ANOVA and *t* test).

BDNF levels are decreased in patients for stressful conditions and depressive disorders. After treatment with antidepressants, BDNF levels are increased and were closer to baseline[16,21]. In order to eliminate patient's stress and anxiety, an anxiolytic might be routinely administered as premedication during the preoperative period. However, in our study, anxiolytic were not given to the patients to achieve standardization between groups. The decreased of BDNF levels with general anesthesia in the patient without premedication might be due to eliminating the patient's stress and anxiety during the preoperative period with the anesthesia induction. But BDNF levels's changes did not correlate to stress hormones. Therefore, BDNF levels's change was thought due to depressant effect of general anesthetics.

In addition to the above results, BDNF has also been found to be upregulated in models of neuropathic and inflammatory pain and has an antinociceptive effect on visceral pain[22-24]. It has been shown that BDNF is upregulated at the dorsal root ganglion and spinal cord with the surgical incision applied to hind paw on rats and this increase can be prevented by ipsilateral sciatic nerve bloc[25]. Our findings may suggest that the BDNF levels changes which developed in the general anesthesia was not developed in the spinal anesthesia likely due to the preventative effects of spinal anesthesia on transmission of painful stimuli. But BDNF levels did not change even after motor and sensory blocks disappear in spinal anesthesia group. Therefore, serum BDNF level change in general anesthesia was thought brain and consciousness.

Cortisol is a parameter of the stress response. In a report[26] that examined the effects of general and epidural anesthesia on cortisol, the cortisol levels, 30 minutes after the start of surgery and when the skin was closed, were significantly high in the patients received general anesthesia compared to the patients received the epidural anesthesia. It has been shown that the spinal anesthesia added to the general anesthesia causes more decreased serum cortisol levels compared to epidural anesthesia added to the general anesthesia[27]. We detected that serum cortisol levels were higher in patients who received general anesthesia compared to the patients who received spinal anesthesia.

In a study[28] that examined the effect and clearance of insulin during general and epidural anesthesia, it was determined that general anesthesia decreased the clearance and the hypoglycemic effect of insulin whereas epidural anesthesia did not effect at all. In our investigation we also found no significant difference in serum insulin levels among the groups. In a study[29] that examined two general anesthesia techniques there was no significant difference among the groups for insulin levels; however, it was observed that postoperative insulin levels were increased in some groups. In our research insulin levels during the postoperative period were significantly increased compared to the intraoperative period in the patients received the general anesthesia.

In a study which investigated the effects of general anesthesia on the serum glucose levels[29] it was determined that the glucose levels were increased after the anesthesia induction. It was observed that serum glucose levels did not change in patients that received spinal anesthesia[30]. In a study[31] that compared the both methods, it was stated that serum glucose levels were increased with the general anesthesia and did not change with the spinal anesthesia. We observed that serum glucose levels were also gradually increased after anesthesia induction for the patient received general anesthesia and there was a slight increase in serum glucose levels after recovery for patients who received spinal anesthesia.

It has been shown that BDNF-mediated synaptic maturation was impaired in neurons exposed to high levels of glucocorticoids[32,33]. Another investigation[34] studied the relationship between serum BDNF levels, cortisol levels and cognitive functions in depressive disorders and determined a relationship between serum BDNF levels and morning cortisol levels.

Conclusions

In our researchy, while there were significant changes on the serum BDNF levels in the patients received general anesthesia there were no changes on the serum BDNF levels in the patient with spinal anesthesia. There were also no significant correlation between the serum BDNF levels and the parameters that reflect the stress response. Therefore, it is suggested that the levels of BDNF are changed by the effect of general anesthesia. Also, our study was performed on young adults patients and if the study was performed in pediatric patients, we may have found more effects on serum BDNF levels because of the neurotoxic effects of anesthetics. This investigation is important because it is one of the first

research to show the relationship between BDNF and anesthesia. In future, BDNF can be used as a biochemical parameters of anesthesia/sedation level. However, comprehensive studies are needed to assess the relationship between anesthesia and neurotrophin.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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