EVALUATION OF THE RELATIONSHIP BETWEEN SERUM YKL-40, HMGB1, BDNF, NGF LEVELS, AND COGNITIVE FUNCTIONS IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

Koroner Arter Bypass Greft Ameliyatı Geçiren Hastalarda Serum YKL-40, HMGB1, BDNF, NGF Düzeyleri ve Bilişsel Disfonksiyonlar Arasındaki İlişkinin İncelenmesi

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ABSTRACT

Objective: Postoperative cognitive dysfunction (POCD) is characterised by symptoms that may inhibit planning, such as dementia, memory loss, attention deficiency and behavioural impairment. Although it frequently occurs after cardiac surgery, all manner of surgery can cause POCD. In this manuscript, we aimed to show the existence of a correlation between high-mobility group box 1 (HMGB1), YKL-40, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and cognitive functions.

Material and Methods: Twenty-four patients who underwent coronary artery bypass graft (CABG) were analysed prospectively. Preoperative 2nd and postoperative 5–7th day blood samples were collected, and a cognitive test was performed synchronously. Correlations between YKL-40, BDNF, NGF and HMGB1 levels and cognitive test score (CTS) were examined.

Results: We found a significant postoperative decrease in NGF ($p = 0.010$). There was a positive correlation between postoperative NGF and postoperative CTS ($r = 0.542$, $p = 0.006$). Postoperative memory score increased ($p = 0.001$), but orientation and vigilance scores decreased ($p = 0.035$ and $p = 0.025$, respectively). There were also self-reliant positive correlations between preoperative and postoperative CTS ($r = 0.825$, $p < 0.0001$), preoperative and postoperative HMGB1 ($r = 0.529$, $p = 0.008$) and preoperative and postoperative NGF scores ($r = 0.454$, $p = 0.026$). Postoperative CTS had a negative correlation with age ($r = -0.447$, $p = 0.029$), duration of operation ($r = -0.506$, $p = 0.012$) and cardiopulmonary bypass (CPB) ($r = -0.403$, $p = 0.039$).

Conclusion: The data in this study suggest that NGF can be a notable parameter in POCD, and HMGB1 may be a crucial marker in heart disorders. To define appropriate diagnosis and treatment strategies, it is essential to detail the relationship between cognitive functions, neuroinflammation and neurotrophic factors.

Keywords: *Coronary Artery Bypass Grafting; NGF; Postoperative Cognitive Dysfunction; Cognitive Impairment*

ÖZET

Amaç: Postoperative bilişsel disfonksiyon (POBD) demans, dikkat eksikliği, hafıza ve davranışsal bozulmalar, planlama yapamama gibi semptomlarla karakterize bir tablodur. Pek çok cerrahi işlem sonrası rastlanabilmekle beraber kardiak cerrahi sonrası görülme sıklığı fazladır. Bu çalışmada, nöroinflamasyon ve nörotrofik faktör parametreleri ile kognitif test arasındaki korelasyon varlığını göstermeyi amaçladık.

Gereç ve Yöntemler: Elektif koroner arter bypass greft ameliyatı olan 24 hasta prospektif olarak incelendi. Preoperatif 2.gün ve postoperatif 5-7.gün serum örnekleri alındı ve eş zamanlı olarak kognitif test uygulandı. YKL-40, BDNF, NGF ve HMGB1 ile kognitif test skorları arasındaki korelasyon değerlendirildi.

Bulgular: Çalışma sonucunda NGF değerinde postoperatif anlamlı düşüklük bulunmuştur. (p=0,010). Postoperatif NGF ile postoperatif kognitif test arasında pozitif korelasyon saptanmıştır. (r=0,542, p=0,006). Bellek puanı postoperatif artmış (p=0,001),oryantasyon ve uyanıklık ise postoperatif azalmış olarak bulundu. (p=0,035 ve p=0,025, sırasıyla).Preoperatif ve postoperatif HMGB1 (r=0,529, p=0,008), NGF (r=0,454, p=0,026) ve kognitif test skorları (r=0,825, p <0,0001) arasında ise pozitif korelasyon saptandı. Postoperatif kognitif test skorları ile yaş (r=-0,447, p=0,029), kardiyopulmoner bypass (r=-0,403, p=0,039) ve operasyon süresi (r=-0,506, p=0,012) arasında ise negatif korelasyon görüldü.

Sonuç: Çalışmamız sonucunda NGF 'nin POBD değerlendirmesinde önemli bir parametre olabileceğine dair veri elde edilmiştir. HMGB1'in kardiak hastalıklarda bir marker olarak araştırılması gündeme gelmiştir. Kognitif fonksiyonlar ile nöroinflamasyon ve nörotrofik parametreler arasındaki ilişkinin detaylandırılmasının uygun tanı ve tedavi stratejilerinin belirlenmesi açısından önemli olduğunu düşünüyoruz.

Anahtar Kelimeler: *Koroner Arter Bypass Greft; NGF; Postoperatif Komplikasyon; Kognisyon*

INTRODUCTION

Cardiovascular diseases remain one of the major causes of mortality. Coronary artery bypass graft (CABG) is a frequently performed surgical procedure related to these diseases (1).

Studies indicate that approximately 15% of patients who underwent CABG return to the hospital after being discharged with diagnoses such as postoperative infections, cardiac failure, dysrhythmia and neurological conditions (2-4). Neurological complications of CABG are estimated to 1% – 5% (5). Postoperative cognitive dysfunction (POCD) is a central nervous system failure that results in impaired linguistic ability, memory and psychomotor speed. It also contributes to limited attention, memory loss and social impairment without specific signs of injury in the nervous system (6,7). One study examined the cerebral side effects experienced by older individuals who have undergone surgical procedures with anaesthesia and reported that individuals who underwent surgeries experienced postoperative symptoms such as dementia, the inability to recognise their relatives, a decline in physical activity in daily life, confusion and impaired interest in family members. Notably, these individuals did not exhibit any neurological complaints before the surgeries (8).

Neuroinflammation and its relationship with POCD by inhibiting neurogenesis, an essential component of cognitive functions, are commonly assumed, and neurotrophic factors (NF) play a vital role in sustaining neurogenesis (9). Nerve growth factor (NGF) affects the growth and survival of peripheral sensory and sympathetic neurons. Previous studies have shown that NGF reduces neuronal damage in rats before and after forebrain ischemia (10).

Brain-derived neurotrophic factor (BDNF) was first discovered in 1982 via purification from pig brains (11). Studies emphasise lower BDNF levels in cognitive functional failure–related disorders (12,13).

High-mobility group box 1 (HMGB1) is a tissue damage–related alarmin family member. HMGB1 is released in the blood in a delayed and has a periodic pattern of long-term continuous elevation (14). Research about HMGB1 underlines its relationship with microvascular thrombosis, acute coronary syndrome and cerebrovascular events (15). Studies suggest that postoperative elevation of HMGB1 may cause cognitive dysfunction (16).

YKL-40, known as chitinase-3-like protein 1, a glial inflammatory marker, was higher in older individuals and patients with Alzheimer's (17-19). One study showed a negative correlation between YKL-40 and cortical thickness and tau protein–like effect of YKL-40 in the brain (20). YKL-40 is accepted as a biomarker in cardiovascular disease prognosis due to its role in inflammation (21).

We aimed to define the correlation between serum BDNF and NGF for neurotrophic factors and HMGB1 and YKL-40 for neuroinflammation. The Montreal Cognitive Test (MoCA) was used to evaluate cognitive function (22).

MATERIAL AND METHODS

Twenty-four volunteer patients who underwent CABG electively between December 2019 and December 2020 were evaluated following ethics committee approval. The study protocol was approved by Ankara City Hospital No:1 Medical Research Scientific Ethics Committee (date: 03.10.2019, no: E1/067/2019).

Informed consent was obtained from all patients. We planned to include patients aged 30 to 80 and established the following exclusion criteria: current neurological disease, transient ischemic attack, history of head trauma, diagnosis of a neuroinflammatory illness known to cause cognitive dysfunction, active infection and fever, illiteracy and failure to establish adequate cooperation with the patient.

We measured HMGB1, YKL-40, BDNF and NGF in the volunteer patients' serum taken on the preoperative 2nd day and postoperative 5–7th days. We also investigated the correlation between each marker and the MoCA test, which was administered to volunteers by the same tester (B.K.) after sampling. Additional parameters included duration of operation, hospitalisation, postoperative intensive care unit stay, CPB time, cross-clamp (CC) time, perioperative blood product transfusion, age, sex, ejection fraction, comorbidity, reoperation during hospitalisation and number of diseased vessels.

The serum samples were kept at room temperature for 2 hours in a standard yellow capped tube then centrifuged at 3000 rpm for 10 minutes and stored at

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-80 °C until sample analysis (AFG Bioscience Human Nerve Growth Factor ELISA kit EK:711226, AFG Bioscience Human Brain-Derived Neurotrophic Factor ELISA kit EK:700371, AFG Bioscience Human High Mobility Group Box 1 Protein ELISA kit EK:716341 and AFG Bioscience Human Cartilage glycoprotein 39 ELISA kit EK:700392). The coefficients of variation of the kits were given as less than 8% and 10% (in-study and inter-study, respectively). The washing processes performed in the ELISA analysis were carried out using an ELx50 Bioelisa Washer, Bio-Tec. Instruments, Inc. An ELx800 UV Universal Microplate Reader, Bio-Tec. Instruments, Inc. was used for absorbance readings.

The Turkish version of MoCA was administered to volunteers and used as a rapid screening test for cognitive impairment and the parameters it evaluates with various subtests, including memory (short-term memory recall task and delayed recall (5 points all)), language (3-item confrontation naming task (3 points) and repetition of 2 syntactically complex sentences repetition (2 points)), visual structuring skills (three-dimensional cube copy (1 point) and a clock-drawing task (3 points)), executive functions (Trail-Making Test B (1 point), a phonemic fluency task (1 point) and a 2-item verbal abstraction task (2 points)), attention-concentration (digits forward and backward tasks (1 point each), letter detection by tapping (1 point), and a serial backward subtraction task (3 points)) and orientation (orientation in time and place (6 points)) (23). An individual can get a maximum of 30 points. Scoring 21 points or higher indicates good cognitive function (24-25).

Statistical Analysis

Statistical analysis was performed using the specified tests in SPSS 20.0 (SPSS, Chicago, IL, USA). Data are given as median (25%–75%), (minimum–maximum), n (%). A p-value of less than 0.05 was considered statistically significant in all analyses. The Kolmogorov–Smirnov test was applied to the measurable parameters to determine whether the distribution was normal or abnormal. MoCA and other data were evaluated with a Wilcoxon signed-rank test in intragroup evaluations. The correlation between the parameters measured by MoCA was evaluated using Spearman correlation. A Spearman correlation coefficient (r) < 0.20 and values close to zero indicated no significant relationship or minimal correlation. We categorised the relationships between levels as mild (0.2–0.39), moderate (0.4–0.59), severe (0.6–0.79) and very severe (0.8–1).

RESULTS

The median age of the patients was 65.00 (56.25–69.75) (48–73), and there were 23 male patients and 1 female patient. The other demographic and perioperative characteristics of the patients are presented in Table 1. Preoperative and postoperative NGF, YKL-40, BDNF and HMGB1 levels are summarised in Table 2. There was a significant decrease in postoperative NGF levels from their preoperative values (p = 0.010). There were

Table 1. Patients' demographic and perioperative data (mean±Standart Derivation (min-max. n (%))

	Median (25%-75%) (min-max) n =24
Age	65.00 (56.25-69.75) (48-73)
Sex (Male/Female)	23/1
Ejection fraction	60.00 (50.00-60.00)(40-65)
Diabetes mellitus (yes/no)	14 (58.3) /10 (41.7)
Other comorbidities (yes/no)	21(87.5) /3(12.5)
Duration of operation(minute)	375.00 (360.00-420.00) (300-480)
Duration of cardiopulmonary bypass(minute)	113.00 (99.75-137.25 (51-177)
Duration of cross-clamp(minute)	76.00 (60.50-96.25) (37-142)
Duration of intensive care unit stay (hour)	72.00 (48.88-96.00) (24-144)
Duration of hospitalization (day)	12.00 (11.00-13.75) (5-30)
Intraoperative transfusion	2.00 (1.00-3.00) (0-4)
Total transfusion	7.00 (6.00-7.75) (3-21)

min: minimum, max: maksimum

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no significant differences between the preoperative and postoperative values of YKL-40, BDNF and HMGB1 (p = 0.715, p = 0.543, and p = 0.465, respectively).

The patients' preoperative and postoperative MoCA scores and subgroup data are detailed in Table 3.

There was no significant difference in the preoperative and postoperative MoCA scores. When examining subgroups of MoCA, the mean of the postoperative word repetition test for evaluating memory assessment was significantly higher than that of the preoperative test (p = 0.001). For orientation assessment, volunteers were requested to respond with the name of the city they were in, as well as the date and current day. The median of the postoperative orientation assessment was considerably lower than the median of the preoperative evaluation (p = 0.035). Vigilance by letter tapping, which assesses attention-concentration, was remarkably less than the preoperative score. (p = 0.025). The other subgroups of the MoCA assessment showed no remarkable differences.

Table 2. Patients' YKL-40, BDNF, HMGB1 and NGF data (median (25%-75%) (min –max))

	Preoperative (n=24)	Postoperative (n=24)	P
YKL-40(ng/mL)	63.60 (55.63-85.60) (36.9-159.4)	62.65 (54.73-79.50) (36-140.9)	0.715
BDNF (pg/mL)	1434.50 (1279.50-1559.00) (664-2961)	1243 (1083.75-1814.00) (754-6381)	0.543
HMGB1 (pg/mL)	1186.00 (570.25-1911.75) (40-4589)	1305.00 (419.25-2613.25) (40-6066)	0.465
NGF (pg/mL)	1051.50 (674.25-1387.00) (418-1846)	743.00 (502.25-932.00)* (343-2412)	0.010

YKL-40: Chitinase-3 like-protein-1, BDNF: Brain-derived neurotrophic factor, HMGB1: High-mobility group box 1, NGF: Nerve growth factor, *: p<0.05 (compared to preoperative), min: minimum, max: maksimum

Table 3. The data of preoperative and postoperative MoCA test scores ((median (25%-75%), min-max)) and subgroups (median (25%-75%))

	Preoperative (median (25%-75%)) (min-max) (n=24)	Postoperative (median (25%-75%)) (min-max) (n=24)	P
MoCA	20.00 (16.00-23.00) (12-26)	20.00 (18.00-22.00) (13-30)	0.135
Executive functions			
Trail-Making Test B	0.00 (0.00-0.75 (0-1)	0.00 (0.00-1.00) (0-1)	0.655
Phonemic fluency task	0.00 (0.00-1.00) (0-1)	0.00 (0.00-1.00) (0-1)	1.000
2-item verbal abstraction task	1.00 (0.00-1.00) (0-2)	0.00 (0.00-1.75) (0-2)	0.655
Visual structuring skills			
Three-dimension cube copy	1.00 (1.00-1.00) (0-1)	1.00 (1.00-1.00) (0-1)	1.000
Clock drawing task	3.00 (2.25-3.00) (0-3)	3.00 (2.25-3.00) (0-3)	0.380
Language			
3-item confrontation naming task	3.00 (2.00-3.00) (1-3)	3.00 (2.00-3.00) (1-3)	0.527
Repetition of 2 syntactically complex sentences	1.00 (1.00-2.00) (0-2)	1.00 (0.00-2.00) (0-2)	0.564
Memory			
Short-term memory recall task and delayed recall test	0.00 (0.00-1.75) (0-3)	1.00 (0.00-3.75)* (0-5)	0.001
Attention-concentration			
Digits forward	0.50 (0.00-1.00) (0-1)	1.00 (0.00-1.00) (0-1)	0.180
Digits backward	1.00 (0.00-100) (0-1)	1.00 (1.00-1.00) (0-1)	0.157
Letter detection by tapping	1.00 (1.00-1.00) (1-1)	1.00 (1.00-1.00)* (0-1)	0.025
Serial backward subtraction task	2.00 (2.00-3.00) (0-3)	2.00 (2.00-3.00) (0-3)	1.000
Orientation			
Time, place, date	6.00 (6.00-6.00) (5-6)	6.00 (5.00-6.00)* (4-6)	0.035

*p<0.05(compared to preoperative), min: minimum, max: maksimum, MoCA: Montreal Cognitive Test

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Preoperative MoCA scores and correlations with other parameters—YKL-40, BDNF, HMGB1, NGF, age, ejection fraction, diabetes mellitus and other comorbidities-showed no notable difference. However, there was a positive moderate correlation between postoperative NGF and postoperative MoCA (r = 0.542, p = 0.006). In contrast, there were negative correlations between postoperative MoCA and age, duration of operation and CPB, as seen in Table 4. (r = -0.447, p = 0.029, r = -0.5506, p = 0.012, r = -403, and p = 0.039, respectively). It was found that there were self-reliant moderate relationships between volunteers' preoperative HMGB1 levels and postoperative HMGB1 levels, and volunteers ' preoperative and postoperative NGF levels (r = 0.529, p = 0.008; r = 0.454, and p = 0.026, respectively). There was also a very severe relationship between preoperative MoCA and postoperative MoCA scores (r = 0.825, p < 0.0001).

DISCUSSION

We hypothesised that neuroinflammation parameters would increase after the operation and that neurotrophic factors and MoCA scores would decrease. We found a significant decrease in postoperative NGF values caused by neuronal damage based on the neuroinflammatory process. The literature shows a relationship between decreases in systemic and cerebral NGF levels after stress exposure and exogenous NGF administration in neurodegenerative diseases (9). Although there are currently no definitive data to explain the decline in NGF levels after cardiac surgery that we noted, one possible explanation is neuroinflammation after CABG. In light of our results, we believe that NGF can be used as a marker to evaluate cognitive functions in the postoperative period, but further research is necessary.

The symptoms of POCD may appear without any evidence of injury and can be observed throughout an extensive spectrum (6,7). For this purpose, although there was no notable decrease in postoperative MoCA scores compared to preoperative MoCA scores, we wanted to comment on the other results we gained from our research.

The significant decrease in postoperative tests of vigilance and orientation is consonant with our hypothesis, as well as the literature data showing a relationship between NGF and REM sleep and wakefulness (26). More research investigating why this decline does not occur in other cognitive function tasks is needed.

Table 4. The correlation of postoperative MoCA scores and other parameters

	r	P
YKL-40(ng/mL)	-0.238	0.262
BDNF (pg/mL)	0.347	0.096
HMGB1 (pg/mL)	0.223	0.294
NGF (pg/mL)	0.542	0.006*
Age	-0.447	0.029*
Ejection fraction	0.071	0.741
Diabetes mellitus	-0.092	0.668
Other comorbidities	-0.307	0.144
Duration of operation (minute)	-0.506	0.012*
Duration of cardiopulmonary bypass (minute)	-0.403	0.039*
Duration of cross-clamp(minute)	-0.262	0.216
Number-vessel bypass	-0.361	0.083
Duration of intensive care unit stay (hour)	0.328	0.118
Duration of hospitalization (day)	-0.316	0.132
Intraoperative transfusion	-0.322	0.125
Total transfusion	-0.084	0.697

YKL-40: Chitinase-3 like-protein-1/BDNF: Brain-derived neurotrophic factor/HMGB1: High-mobility group box 1/ NGF: Nerve growth factor, min: minimum, max: maksimum

MoCA was administered two days before surgery and 5–7 days after surgery. The intervening time's relative proximity may explain the scores of the preoperative and postoperative controls. Word repetition question evaluates memory functions in the MoCA and its score significantly increased in the postoperative control. Similar to our research, in the literature, the word repetition score assessing memory function, which has been the main subject of varied studies in cardiac surgery, significantly increased in the postoperative period in contrast to the score for other questions (27,28). A study highlighted the difference in word repetition during short-term follow-up between patients who underwent CABG and those with atherosclerotic heart disease (AHD) who did not have CABG (29). The study implied that the test application field, AHD severity, and time could be related to different results. Longer follow-up, such as 2 or 3 months after surgery, should be designed to obtain more specific outcomes related to this factor (30). Volunteers' preoperative stress levels might also be related to increased postoperative word repetition scores. The literature supports stress-induced alterations in gene expression and action variations, although the precise mechanisms have not been definitively elucidated (31).

There is research on MoCA's capability to define cognitive reserve. 'Cognitive reserve' is described as 'adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult (32). It may be related to the very severe relationship between preoperative and postoperative MoCA scores in our paper. Considering the negative correlation between age and postoperative MoCA, age, education and lifestyle might help this relationship.

The operation type, hypoperfusion, cerebral microembolisms, duration of hospitalization, operation, CC and CPB are thought to affect POCD (33). We found a negative correlation between the duration of operation and CPB with postoperative MoCA, as hypothesised.

YKL-40 did not significantly change, contrary to our hypothesis. An exciting paper about cardiac surgery and revascularisation markers, including YKL-40 has been published (34). The sampling time was similar to our study, but they found a significant elevation of YKL-40 levels on the 7th day and an average level in 3 months. Additionally, there was an inspirational but not very detailed comment by various researchers on Malmeström's paper that highlighted that YKL-40 could have differed in different stages of neuroinflammatory disease due to immunosuppressive therapy (35). On-pump cardiac surgery might have affected our levels through immunosuppression.

Unexpectedly, there was neither a notable elevation of the postoperative HMGB1 level nor any correlation between other parameters. In light of these findings, we comment on the moderate relationship between the preoperative and postoperative HMGB1 values related to HMGB1's potential as a cardiac marker. Our HMGB1 values were measured by ELISA, and four participants had rheumatological comorbidities. Having a rheumatological condition before surgery affects HGMB1's release pattern after surgery.

Explaining the relationship between cardiac surgery and POCD, especially considering factors other than CPB, is needed. We believe POCD studies should be detailed, such as associating the type of prosthesis used in patients undergoing valve replacement or the existing difference between arterial and venous grafts in individuals who have undergone CABG surgery. Urgency of the operation, the number of lesions, and differences in the graft material used should be examined in future examinations.

One limitation of the current study is that we performed the procedure in a single centre with limited patients. We originally planned for our study to have 45 patients and four time-point controls: preoperative 2nd day, postoperative 5–7th days, postoperative 3rd week and postoperative 2nd month. Unfortunately, 3 months into the study, the COVID-19 pandemic hit our country. Travel restrictions affected the postoperative 3rd week and 2nd month controls. Under these circumstances, we had to limit the number of volunteers and the follow-up period to collect data from the beginning. We had to change the study protocol and the number of volunteers. The relative proximity of the intervening time mentioned before may explain the scores of the preoperative and postoperative controls.

For these reasons, the test application time can be considered another limitation of our study.

CONCLUSION

Our study showed a significant decrease in postoperative NGF and a positive correlation between postoperative MoCA and NGF. A moderate relationship between preoperative and postoperative NGF levels was also observed; given this, NGF might be an essential parameter for POCD assessment. A very severe relationship between preoperative and postoperative MoCA scores was noted, and a correlation of postoperative NGF with postoperative MoCA score was also found. We also noted a moderate relationship between preoperative and postoperative HMGB1, which may be a sign of HMGB1's possible relationship with cardiac diseases. Postoperative memory scores increased, but orientation and vigilance scores decreased. Future studies are necessary for the appropriate diagnosis and treatment of POCD.

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The authors declare that they have no competing interests.

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