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Evaluation of the Effects of the Heart-Lung Machine on the Plasma Beta-2 Microglobulin Level

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ABSTRACT:
Purpose: In this study, it was aimed to investigate whether beta-2 microglobulin (β2M) blood plasma level is affected by cardiopulmonary bypass (CPB) and its effects on prognosis in surgeries performed using a heart-lung machine.
Material and Methods: The study was carried out on 33 patients who underwent cardiac surgery using a heart-lung machine in the cardiovascular surgery department of Sivas Cumhuriyet University. Plasma β2M levels were evaluated in peripheral venous blood samples taken just before the operation, thirty minutes after connecting to the heart-lung machine, and at the twenty-fourth postoperative hour.
Results: It was observed that a high β2M level was associated with long intensive care and hospital stay, prolonged intubation, increased inotrope requirement, and blood product use (P<.001). In addition; advanced age, tobacco use, hyperlipidemia, and hypertension were also associated with high β2M levels (P<.001). It was observed that the heart-lung machine did not affect the plasma β2M level (P=0.843).
Conclusion: The heart-lung machine did not affect the plasma β2M levels. However, it seems likely that high β2M levels can be used as a predictive marker for poor prognosis in open heart surgery.
Keywords: *Beta-2 microglobulin, Cardiac surgery, Cardiopulmonary by-pass machine, Open heart surgery*

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INTRODUCTION

Former studies for beta-2 microglobulin (β2M) were generally focused on kidney diseases, leukemias, and inflammatory diseases. In recent years, many studies have been published on the relationship between cardiovascular diseases and β2M. β2M is a protein located on the surface of all nucleated cells. β2M is released from the cell surfaces mostly from lymphocytes and passes into the plasma. Due to its low molecular weight, it is completely filtered by glomerular filtration and is excreted in the urine without being reabsorbed by tubular cells. The level of β2M is significantly increased in renal diseases that decrease the glomerular filtration rate, patients on dialysis, chronic inflammatory diseases, liver or malignant diseases, multiple myeloma, B-cell lymphoma and chronic lymphocytic leukemia (Bethea et al., 1990; Tomlinson, 1992; Wong, 1999). Although the normal blood plasma level of β2M has not been standardized, it is usually in the range of 1.1-2.4 mg/L. (Johnson et al. 1980). As atherosclerosis is an inflammatory cascade like the diseases mentioned above, a large number of studies have also been done on the relationship between atherosclerotic vascular diseases and β2M (Amighi et al., 2011). During cardiopulmonary bypass, blood cells are in contact with foreign matter and surfaces. Contacting with non-endothelial surfaces activates inflammatory response and increases the release of many vasoactive mediators (Çalışal, 2013). In this study, we investigated the plasma β2M level in on-pump heart surgery. In addition to the effects of the

heart-lung machine on plasma β2M level, we also found some surprising findings in the study.

MATERIAL and METHODS

Purpose and Type of the Study

This study is a research article examining prospective data. This study, it was aimed to investigate the possible changes in β2M blood plasma level and its possible effect on prognosis in cardiopulmonary bypass surgery performed by using a heart-lung machine.

Sampling and participant

Between June 2019 and January 2020 at Sivas Cumhuriyet University, Faculty of Medicine, 33 patients who operated by using a heart-lung machine for any reason were included in the study.

Data Collection Tools

Written informed consent was obtained from all patients. Peripheral venous blood sampling was taken three times from the patients. Just before starting the operation, thirty minutes after being connected to the heart-lung machine, and twenty-four hours after the operation. The samples were immediately sent to the biochemistry laboratory and blood plasma β2M levels were studied. Patients younger than 18 years of age, with chronic kidney disease, on hemodialysis, chronic inflammatory diseases, multiple myeloma, B-cell lymphoma, or chronic lymphocytic leukemia were excluded from the study. Huang and colleagues, who conducted a study on the β2M level, divided the patients into four groups according to the results (Huang et al 2022). On the other hand, Cheung and colleagues, found the mean β2M level to be 2 mg/L in their study (BMY et al., 2016). We designed our study in two groups. We grouped them as β2M level <2 mg/L as the 1st group and as ≥2 mg/L as the 2nd group.

Statistical Analysis

Statistical analysis was done by using the SPSS 24 package statistical program (StataCorp LP, College Station, TX, USA) software package. In the study, continuous variables were expressed as mean ± SD and categorical variables as frequency and percentage (%). The Kolmogorov-Smirnov test was performed for normally distributed variables. Inter-group differences were evaluated using the Student t-test for normally distributed continuous variables and the Mann-Whitney U test for variables that did not show normal distribution. Pearson chi-square test was used for the comparison of categorical variables. A P value of <.05 was considered statistically significant.

Ethical Approval

The study was started after the decision of the ethics committee of the Medical Faculty of Sivas Cumhuriyet University, numbered 2019-05/07.

RESULTS

The heart-lung machine had no significant effect on intraoperative and postoperative β2M levels (Table 1). As in previous studies, patients were divided into groups according to β2M level. Significant differences were observed in terms of many parameters. According to the preoperative data of the patients, it was seen that advanced age, tobacco use, hypertension, hyperlipidemia, using angiotensin-converting enzyme (ACE) inhibitors, using angiotensin receptor blockers (ARBs) and using beta blockers were associated with high β2M levels. However, considering that already hypertensive patients are taking antihypertensive treatments, it does not seem possible to associate drug use with high β2M levels. There was no significant difference was observed between other preoperative data (Table 2). When the intraoperative data were examined, no significant difference was observed between the two groups due to types of surgery, total CPB time, and X-clamp times (Table 3). Perhaps the most interesting results of the study were obtained from the postoperative data. High β2M levels were closely related with postoperative long intubation time, prolonged intensive care and hospitalization stay, increased need for inotropes, and increased use of blood and blood products (Table 4). In another data set in which the laboratory and echocardiographic data of the patients were examined. There was no significant difference was found between the two groups in terms of any parameter (Table 5).

Table 1: Effect of cardiopulmonary bypass machine on plasma Beta-2 microglobulin level

Groups	Preoperative beta-2 level mg/L (mean)	During the cardiopulmonary bypass beta-2 level mg/L (mean)	Postoperative beta-2 level mg/L (mean)	P value
Group 1 (beta-2 plasma level <2 mcg/mL) (n=15, 45.4%)	1.53±0.23	1.37±0.64	1.26±0.47	0.852
Group 2 (beta-2 plasma level ≥2 mcg/mL) (n=18, 54.6%)	2.90±1.04	2.74±1.55	2.45±1.14	0.573
Mean beta-2 plasma level mcg/mL (n=33, 100%)	2,27±1.03	2,12±1.40	2,09±1.08	0.843
P value	**<.001**	**<.001**	**<.001**	

Table 2: Preoperative data of patients

Preoperative data (n, %)	Group 1 (beta-2 plasma level <2 mg/L) (n=15, 45.4%)	Group 2 (beta-2 plasma level ≥2 mg/L) (n=18, 54.6%)	P value
Age (years)	56±17.0 (25-77)	65.8±9.0 (46-80)	***<.001***
Female (n, %)	6 (40)	5 (27.7)	0.054
Male (n, %)	9 (60)	13 (72.3)	
Tobacco use (n, %)	4 (26.6)	10 (55.5)	***<.001***
Alcohol use (n, %)	1 (6.6)	2 (11.1)	-
BMI (kg/cm2)	28.07±3.27	28.76±4.62	0.596
Hypertension (n, %)	6 (40)	11 (61.1)	***<.001***
Diabetes (n, %)	6 (40)	9 (50)	0.186
Hyperlipidemia (n, %)	5 (33.3)	9 (50)	***<.001***
COAD	3 (20)	3 (16.6)	0.892
Peripheral arterial disease	2 (13.3)	4 (22.2)	0.563
ACE inhibitors use	1 (6.6)	6 (33.3)	***<.001***
Diuretic use	3 (20)	5 (27.7)	0.765
ARBs use	2 (13.3)	5 (27.7)	***<.001***
Beta-blocker use	4 (26.6)	8 (44.4)	***<.001***
CCB use	2 (13.3)	4 (22.2)	0.052
Warfarin use	1 (6.6)	2 (11.1)	-
Antiagregan use	7 (46.6)	10 (55.5)	0.936

ACE: Angiotensin-converting enzyme, **ARBs:** Angiotensin receptor blockers, **BMI:** Body-mass index, **COAD:** Chronic obstructive airways disease, **CCB:** Calcium channel blocker

Table 3: Intraoperative data of patients

Intraoperative data	Group 1 (beta-2 plasma level <2 mg/L) (n=15, 45.4%)	Group 2 (beta-2 plasma level ≥2 mg/L) (n=18, 54.6%)	P value
Aortocoronary bypass grafting (n, %)	11 (73.3)	14 (77.7)	0.858
Aortic valve replacement (n, %)	1 (6.6)	1 (5.5)	-
Mitral valve replacement (n, %)	1 (6.6)	1 (5.5)	-
Adult congenital (n, %)	2 (13.3)	0 (0)	-
Myxoma (n, %)	0 (0)	1 (5.5)	-
Combined cardiac surgery (n, %)	0 (0)	1 (5.5)	-
Total bypass time (minutes)	73.4±15.5	73.2±16.6	0.998
X clamp time (minutes)	46±10.14	49.5±12.02	0.924

Table 4: Postoperative data of patients

Postoperative data	Group 1 (beta-2 plasma level <2 mg/L) (n=15, 45.4%)	Group 2 (beta-2 plasma level ≥2 mg/L) (n=18, 54.6%)	P value
Intubation time (hours)	8.2±2.07	13.5±4.15	***<.001***
Intensive care hospital stay (hours)	1.2±0.40	1.83±0.83	***<.001***
Hospitalization time (days)	6.53±0.88	9.05±3.06	***<.001***
Inotrope requirement (n, %)	3 (20)	13 (72.3)	***<.001***
Fresh frozen plasma requirement (units)	1.93±0.92	3.44±1.11	***<.001***
Erythrocyte suspension requirement (units)	1.66±0.59	4.27±1.09	***<.001***

Table 5: Laboratory and echocardiographic data of the patients

Laboratory and Echocardiographic data	Group 1 (beta-2 plasma level <2 mg/L) (n=15, 45.4%)	Group 2 (beta-2 plasma level ≥2 mg/L) (n=18, 54.6%)	P value
Ejection fraction (%)	52.5±5.3	51.4±5.1	0.974
Blood Urea Nitrogen (BUN) mg/dl	18.20±4.17	21.95±10.02	0.543
Creatinine mg/dl	0.87±0.15	1.13±0.30	0.567
Plasma protein g/L	6.58±0.42	6.52±0.65	0.998
Albumin g/L	4.2±0.42	4.02±0.51	0.823
Serum glutamic oxaloacetic transaminase (SGOT) U/L	25.9±25.7	26.6±18.01	0.754
Serum glutamic pyruvic transaminase (SGPT) U/L	20.1±12.8	20.83±7.08	0.932
Creatine kinase (CK) U/L	67.06±19.2	85.5±76.4	0.532
Creatine kinase-MB (CK-MB) U/L	26.7±68.92	27.5±10.07	0.651
Troponin-T ng/L	1.8±2.7	1.94±2.0	0.865
White blood cell (WBC) 10^9/L	9.23±3.3	8.88±2.7	0.714
Hemoglobin g/dl	13.30±2.38	13.31±1.68	0.994
Hematocrit %	39.57±6.39	39.64±4.72	0.956
Lymphocyte %	23.21±7.87	21.36±8.92	0.848
Lymphocyte count 10^9/L	1.98±0.58	1.80±0.69	0.878
Platelet count 10^9/L	231.67±66.13	221.22±72.48	0.746
International Normalized Ratio (INR)	1.07±0.06	1.06±0.10	0.945

DISCUSSION

β2M is commonly used as a prognostic indicator in kidney diseases, leukemias, and inflammatory diseases. The use of β2M for cardiovascular diseases has gained currency in recent years. Many studies have been published consecutively in the fields of coronary artery diseases, acute myocardial infarction, carotid artery diseases, and heart valve diseases. According to many studies, it is obvious that there is a positive association between higher β2M levels and cardiac outcomes. This is independent of known risk factors as well as renal function and also higher β2M levels were associated with increased risks of infectious and all-cause mortality. Some studies on the association between β2M and cardiac outcomes have reported positive results (Ho et al., 2018) but some of them reported not statistically significant results (Matsui et al.,

2016, Prentice et al., 2013) Amighi and his friends' study showed that β2M could be used as an independent predictor for adverse events in carotid artery disease (Amighi et al., 2011). In a study conducted by Huang et al., it was observed that high β2M levels were associated with an increased risk for cardiovascular disease and all-cause mortality (Huang et al., 2022). Zhang et al. showed that a high β2M level is an independent risk factor in acute coronary syndrome and is associated with coronary stenosis (Zhang et al., 2019). The relationship between high β2M levels and impaired renal function has been known for a long time. However, the relationship between cardiovascular diseases and high β2M levels is significant and has been shown to involve a high risk independent of chronic kidney disease (Shi et al., 2021). β2M levels have been shown to increase independently of troponin levels in acute coronary syndrome (BMY et al., 2016). You et al. showed that β2M can be used as a predictor in determining the severity of coronary artery stenosis (You et al., 2017). In the same study, high β2M was found to be correlated with advanced age, hypertension, low Apo-A, high creatinine and BUN, coronary artery disease, severe coronary artery disease, acute myocardial ischemia, and high Gensini score (You et al., 2017). In another study, a high β2M level in the patient group with the acute coronary syndrome; high creatinine was found to be correlated with advanced age and male gender (Cheung et al., 2017). In our study, we found that high β2M levels were correlated with advanced age. It was also observed to be correlated with hypertension, hyperlipidemia, and tobacco use. There were differences between preoperative drug use of the patients for beta blockers, ACE inhibitors, and ARB inhibitors. However, considering that the patients in this group were already hypertensive, such a difference was possible.

In the studies of Abacioglu and Kaplan, it was seen that coronary slow flow and high β2M level were correlated and it was stated that it could be used as a predictor for slow flow (Abacıoğlu et. al., 2020).

It is known that there is high plasma β2M in chronic renal failure. In a study examining the relationship between cardiovascular diseases, especially in the chronic renal failure patient group, it was shown that the risk of cardiovascular disease increases in cases where plasma β2M exceeds 8.34 mg/L. In this study by Liabeuf et al., it was shown that high β2M can be used as a predictor for cardiovascular diseases even in the chronic renal failure patient group (Liabeuf et al., 2012).

In the study of Wang et al., it was shown that high β2M is a prognostic predictor for cardiovascular events and all-cause mortality risks in elderly patients with isolated systolic hypertension (Wang et al., 2018).

In another study, a β2M level of >1.92 mg/L was found to be associated with major adverse cardiac events. In the same study, it was observed that patients with high β2M levels were rehospitalized more than the β2M level of <1.92 mg/L group due to unstable or progressive angina (Möckel et al., 2015). In the study of Nead et al., they showed that it can be used as a predictor of mortality after coronary angiography when β2M, cystatin C, and C-reactive protein are combined (Nead et al., 2013).

Studies on high β2M levels on mortality and poor prognosis are limited.

There was no in-hospital mortality observed in any of the 33 patients included in our study. However, the group with β2M level ≥2 mg/L had a poor prognosis. Parameters evaluated as poor prognosis signs; long intubation time, long intensive care and hospital stay, high inotrope requirement, and increased blood and blood product use.

Limitations

The most important limitation of the study is the limited population. In addition, a baseline value consisting of healthy volunteers is not available for β2M. So this is another limitation. For this reason, the study should be designed to include large populations and healthy volunteers could provide access to larger data, which could give clearer results.

CONCLUSION

The β2M plasma level is not routinely used in cardiac diseases. However, as a result of the data obtained, a high β2M level can be used as a predictor for predicting the poor prognosis after open heart surgery.

Conflict of Interest

The authors declare no conflict of interest in preparing this article.

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