Orijinal Araştırma / Original Investigation
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Koroner Arter Baypass Cerrahisinde Statinin Antikardiyolipin Antikor Seviyelerine Etkisi

Effect of Statin on Anticardiolipin Antibody Levels in Coronary Artery Bypass Surgery

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ÖZET

AMAÇ: Bu araştırmanın amacı, koroner baypas cerrahisi hastalarında statinin lipit düşürme mekanizması ile diğer yararlı biyolojik etkileri arasındaki bağlantıyı preoperatif statin ile preoperatif, perioperatif ve postoperatif kardiyolipin IgG ve IgM antikor düzeyleri arasındaki ilişkiyi ortaya koyarak incelemektir. Açık kalp cerrahisinde durum sadece kalbin atmasını sağlamak değil, miyokardiyal hasarı önlemek veya en aza indirmektir. Bu nedenle kan elementlerinin ve miyokardın korunması için yeni bir yöntemin ortaya çıkarılması gerekmektedir

GEREÇ VE YÖNTEM: Elektif koroner arter baypas greft cerrahisi planlanan ve araştırma kriterlerimize uyan koroner iskemik hastalığı olan 30 hasta, 40 mg/gün atorvastatin ile standart lipit düşürücü tedavi görenler olmak üzere iki gruba ayrıldı. ameliyattan en az 7 gün önce (grup A) ve ikinci grup ameliyat öncesi düzenli lipit düşürücü tedavi almayanlar (B). Demografik, hemodinamik, laboratuvar ve cerrahi teknik dahil olmak üzere tüm parametreler belgelendi ve kaydedildi.

BULGULAR: Kaydedilen parametreler ve değerler bilgisayar programında şu testler kullanılarak analiz edildi: Kolmogorov-Smirnov testi, Student-t testi, paired-t testi ve Ki-kare testi. Tüm sonuçlar, basit ve daha iyi değerlendirme için 6 tabloda planlanmıştır.

SONUÇ: Bulgular, açık kalp cerrahisinde perioperatif ve postoperatif erken dönemde (ilk 24 saat) statinin yararlı etkilerini desteklemektedir.

Anahtar Kelimeler: açık kalp cerrahisi; statin; antikardiyolipin antikoru

ABSTRACT

OBJECTIVE: The aim of this research is to study the link between lipid lowering mechanism and other beneficial biological effects of statin in patients of coronary bypass surgery by revealing the relation of preoperative statin on pre- , peri- and postoperative cardiolipin IgG and IgM antibody levels. The case in open cardiac surgery was not keeping the heart beating only but preventing or minimizing the myocardial injury. For this reason, a new method for preservation of blood elements and myocardium must be uncovered.

MATERIALS AND METHODS: Thirty patients with coronary ischemic disease whose scheduled to undergo elective coronary artery bypass graft surgery and fitting the criteria for our research were divided in to two groups, those on standard lipid lowering therapy using atorvastatin (40 mg/day) for at least 7 days prior to surgery (group A) and second group those without regular lipid lowering therapy preoperatively (B). All the parameters were documented and recorded, including demographic, hemodynamic, laboratory and surgical technique with outcome.

RESULTS: The recorded parameters and values were analyzed using the following tests in computer program: Kolmogorov-Smirnov test, student t test, paired t test and Chi- square test. All results were scheduled in 6 tables for simple and better evaluation.

CONCLUSION: The findings support the beneficial effects of statin in the perioperative and early postoperative (first 24 hours) in open cardiac surgery.

Keywords: open cardiac surgery; statin; anticardiolipin antibody

INTRODUCTION

First clinical attempts at open heart surgery was reported by Clarence Dennis in 1951, and one year later he successfully used a mechanical pump for supporting left ventricle. Till that time, many researches were conducted on possibility of perfusing the heart with minimal myocardial injury. Possibility of clamping the aorta and pulmonary artery for 2-3 minutes under certain precautions

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was described by Alexis Carrel in 1914. In 1935, A. Carrel and Charles Lindbergh successfully developed a perfusion device by which the heart kept beating for several days but it showed progressive degenerative changes (1).

The case was not keeping the heart beating only but preventing or minimizing the myocardial injury. For this reason, a new method for preservation of blood elements and myocardium must be uncovered. Using of potassium for inhibition of the heart beat was suggested by Hooker in 1929. First experimental study on potassium-based cardioplegia was reported by Melrose in 1955. Principle of blood cardioplegia was renewed by Follette in 1978. Others were studied ischemia-reperfusion injury, damaging effect of surgical trauma, and other inflammatory factors which explain myocardial injury occurring in off-pump cardiac surgery (2). Anticoagulation together with metabolically secured tissue were the goal of all researches. Despite all these measures, cardiac injury still the enemy number one, even in off-pump cardiac surgery.

In open heart surgery, myocardial injury is a multifactorial phenomenon. Myocardium is subjected to microembolism, protease, chemical cytotoxins, hypoperfusion, and activated neutrophiles and monocytes. In another hand, blood exposure to nonendothelial cell (synthetic) surfaces leads to initiation of powerful defense reaction involving plasma protein systems and blood cells (3,4). This inflammatory response to cardiopulmonary bypass affects every organ and tissue within the body. The causes of postoperative cardiac dysfunction are: effects of cardiopulmonary bypass, ischemia-reperfusion injury, direct trauma (manipulation of the heart and pericardial suction), coronary lesions, and preload-afterload maladjustment. Although off-pump cardiac surgery attenuates inflammatory response, it does not prevent it totally (5,6). This inflammatory response may be secondary to the causes other than cardiopulmonary bypass like direct trauma, coronary lesions, heparin, protamine, and other drugs activity.

Cardiolipin is an important component of the inner mitochondrial membrane of metabolically active cells of the heart and skeletal muscle where it constitutes about 20% of the total lipid (7). Extracorporeal circulation related oxidative damage may lead to anticardiolipin formation which is due to structural similarity between cardiolipin and ox-LDL antigenic epitopes (8). In another hand, LDL may involve directly to anticardiolipin induced vascular pathology and may interacts with fibrinolytic pathway (9). LDL may act as a thrombogenic target of anticardiolipin antibodies leading to microembolism and vascular occlusion (10). Anticardiolipin may change thromboxane A2-prostacyclin balance by inducing an interaction between platelet and vascular endothelium, such a change may lead to thrombosis and vasoconstriction (11). Another possible pathway of anticardiolipin related vascular pathology is similar to that of heparin induced thrombocytopenia (12).

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) show its beneficial effects reducing cholesterol biosynthesis and modulation of lipid metabolism (13). Preoperative use of statins was documented to be effective in the reduction of postoperative cardiovascular events in varied cardiac surgery patients (13,14,15). Recent researches revealed that protective effects of statins have been related to biological mechanisms other than lipid lowering action which attenuate adverse surgical outcomes (16,17,18). Non-lipid lowering mechanisms include attenuation of vasoconstriction and endothelial injury (19,20), suppression of inflammatory reactions, and reduce thrombosis (21).

The aim of this research is to study the link between lipid lowering mechanism and other beneficial biological effects of statin in patients of coronary bypass surgery by revealing the relation of preoperative statin on pre-, peri- and postoperative cardiolipin IgG and IgM antibody levels.

MATERIAL & METHODS

Ethical approval was taken from the institutional ethical committee (2009/5-3) and study was designed in accordance to the declaration of Helsinki. Thirty patients with coronary ischemic disease who's scheduled to undergo elective coronary artery bypass graft surgery and fitting the criteria for our research were registered. The criteria included: Age (18-65 years old patients), using cardiopulmonary machine in the open-heart surgery, no preoperative infection, normal levels of liver function and renal function tests, no history of CVA or documented carotid artery disease, and no history of autoimmune or connective tissue disease.

The patients will be divided in to two groups, those on standard lipid lowering therapy using atorvastatin (40 mg/day) for at least 7 days prior to surgery (group A) and second group those without regular lipid lowering therapy preoperatively (B). Demographic characteristics registered

for each patient including: age (year), length (cm), weight (kg), BSA and gender.

Blood samples obtained from central venous cannulas and atraumatic venipunctures at five times: immediately preoperatively, 60 minutes after protamine administration, and on the first, second and fifth postoperative days. For measurements of anticardiolipin IgG and IgM antibody, the blood centrifuged and separated plasma will be stored at -4 °C. Methods of laboratory tests included enzyme immunoassay (ELISA) (Kit Lot 09 40/6 04/1, Generic Assays Gmbh, D-15827, Dahlewitz/Germany).

Anesthesia: started 30 minutes preoperatively by insertion of arterial cannula and central venous catheter (arterial cannula for direct arterial blood pressure monitorization and blood gases analysis sample drawing, central venous catheter for drug administration, central venous pressure monitorization and blood sample drawing). Anesthesia including Remifentanil 1 µcg/kg for one minute which continued after induction as 0,2 µcg/kg/min. then Lidocaine 1 mg/kg for attenuation of sympathetic activity during intubation. Induction using etomidate 0.3mg/kg IV within one minute after that muscle relaxant (pankuronium 0,1 mg/kg IV) will given. After suitable muscle relaxation, intubation performed and maintenance protocol using propofol-remifentanil infusion was applied. Nasopharyngeal probe used for controlling body temperature throughout surgery.

Surgical technique: after suitable cleaning of the surgical field, median sternotomy performed. After preparing of saphenous vein grafts and LIMA harvesting, pericardium incision done and aorto-caval cannulation performed. On cardiopulmonary pump machine, after aortic cross clamp, local cooling and cold blood cardioplegia we completed the coronary distal anastomosis and after that the aortic cross clamp released and heart beating preserved (either spontaneous or with defibrillation). We used aortic side clamp for performing the proximal anastomosis, after which we decreased cardiopulmonary pump flow and stopped it in suitable condition, after that we inserted the drainage tubes. Bleeding control, sternum closure (with wires), subcutaneous closure (with 2/0 Vicryl) and skin closure (with subcutaneous 3/0 Monocryl) done in the routine methods.

Postoperative follow-up: in the ICU with full monitorization (direct arterial blood pressure, central venous pressure, cardiac rhythm, urinary output, amount of blood drainage and blood gas analysis) performed. According to recorded parameters, consciousness condition and general hemodynamic status of the patients extubating and follow-up planned and done. During the peri- and postoperative period, all fluid inlet (IV and oral) and fluid outlet (drainage amount, urine outlet) were recorded.

Statistics

Statistical evaluation SPSS 12,0 was performed using the following tests in computer program. Statistical analysis data were presented as [mean ± standard deviation, n] . As the limit of significance in all statistical analyzes, the value $p< 0,05$ was accepted.

Kolmogorov-Smirnov test was applied to determine whether the normal or abnormal distribution of measured parameters. For those that show normal distribution Student t test was used in independent groups in benchmarking whether there is deference between groups or not. Paired t test was used to compare the data EF, LDL, IgG, IgM in a group with their preoperative measurement values. Gender data evaluation was done using Chi- square test.

RESULTS

In this work undergoing surgery 30 patients took place. In terms of demographic characteristics of patient groups included in our work, there was no statistically significant differences (Table 1). When comparing operation, pump and cross-clamp times and the amount of drainage between groups there was not significant difference, and that the mean of operation, pump and cross- clamp times and the amount of drainage in tow groups was found to be similar (Table 2).

Table 1. *Demographic characteristics of the patients in the group*

	Group A (n=15)	Group B (n=15)	p
Age (year)	57,80±6,57 (42-65)	57,80±5,43 (48-65)	1,000
Length (cm)	167,00±8,04 (156-180)	167,07±8,80 (153-182)	0,983
Weight (kg)	75,73±9,76 (55-90)	78,87±12,13 (60-100)	0,442
BSA	1,85±0,16 (1,56-2,07)	1,88±0,18 (1,57-2,18)	0,611
Gender (m,f)	9/6	8/7	0,71

Mean ±SD (Min- Max), n, m: male, f: female

The mean of LDL measurements were given in table 3. LDL measurements between the groups were found to be similar. Postoperative value in group A found to be evidently decreased in comparison with preoperative value (p=0,013). The mean of EF measurements given in table 4. The mean EF measurements in group B found to be statistically lower than that of group A (p<0,05) (Table 4). In both groups, postoperative measurements were lower than preoperative measurements (p<0,05).

The mean of IgG measurements given in table 5. The IgG measurements during preoperative and pump periods found to be statistically low in group A in comparison to group B (p<0,05) (Table 5). In group A, measurements of all periods found to be significantly high in comparison to preoperative measurements. In group B, measurements of all periods except that of 5. postoperative day found to be significantly high in comparison to preoperative measurements (p<0,05).

The mean of IgM measurements given in table 6. The IgM measurements during preoperative and pump periods found to be statistically low in group A in comparison to group B (p<0,05) (Table 6). In group A, measurements of all periods found to be significantly high in comparison to preoperative measurements. In group B, measurements of all periods except that of 5. postoperative day found to be significantly high in comparison to preoperative measurements (p<0,05).

Table 2. *The parameters of operation, pump, cross- clamp times and the amount of drainage*

	Group A (n=15)	Group B (n=15)	p
Operation Time (hour)	2,47±0,83 (1-4)	2,27±1,10 (1-4)	0,579
Pump Time (min)	73,00±21,44 (46-110)	64,60±28,15 (31-110)	0,366
Cross-clamp Time (min)	43,46±17,60 (23-80)	41,93±21,16 (18-76)	0,831
The Amount Of Drainage (ml)	806,67±149,84 (500-1100)	806,67±217,01 (450-1200)	1,000

Mean ±SD (Min- Max)

Table 3. *The comparison of LDL values between groups*

	Group A (n=15)	Group B (n=15)	p
Preoperative	129,07±33,75 (80-195)	128,73±34,30 (76-178)	0,979
Postoperative	108,27±18,81 +(84-144)	124,00±24,72 (74-160)	0,060

Mean ±SD (Min- Max) | +p<0,05: in comparison with preoperative value

Table 4. *The comparison of EF measurements between groups*

	Group A (n=15)	Group B (n=15)	p
Preoperative	58,67±5,96 (47-69)	53,40±6,76* (40-63)	0,032
Postoperative	56,60±6,10 +(45–65)	49,87±9,33* +(32-64)	0,027

*Mean ±SD (Min- Max) | *p<0,05: in comparison with group A | +p<0,05: in comparison with preoperative findings*

Table 5. *IgG measurements of group A & B*

	Group A (n=15)	Group B (n=15)	p
Preoperative	0,037±0,012 (0.01-0.05)	0,050±0,012 * (0.03-0.07)	0,004
Pump	0,054±0,009 + (0,04-0,07)	0,119±0,117*,+ (0,05-0,53)	0,039
Postoperative 24. hour	0,073±0,014 + (0,05-0,10)	0,098±0,083 + (0,05-0,40)	0,253
Postoperative 72. hour	0,062±0,014 + (0,04-0,09)	0,077±0,048 + (0,04-0,24)	0,259
Postoperative 5. day	0,047±0,012 + (0,02-0,07)	0,062±0,049 + (0,03-0,23)	0,270

**p<0,05: in comparison with group A, +p<0,05: in comparison with preoperative findings*

Table 6. *IgM measurements of group A & B*

	Group A (n=15)	Group B (n=15)	p
Preoperative	0,038±0,010 (0.02-0.06)	0,052±0,015* (0.03-0.08)	0,004
Pump	0,053±0,011+ (0,04-0,08)	0,143±0,140*,+ (0,06-0,64)	0,026
Postoperative 24. hour	0,074±0,010+ (0,05-0,09)	0,103±0,068+ (0,06-0,34)	0,109
Postoperative 72. hour	0,064±0,010+ (0,05-0,09)	0,074±0,031+ (0,05-0,17)	0,205
Postoperative 5. day	0,050±0,008+ (0,04-0,06)	0,055±0,017 (0,03-0,09)	0,230

*Mean ±SD (Min- Max) | *p<0,05: in comparison with group A | +p<0,05: in comparison with preoperative findings*

DISCUSSION

Despite all recorded development and improvement in the surgical techniques, hemodynamic follow-up methods and postoperative care, cardiac surgery still have significant morbidity and mortality rates. Most of the researches concentrated on factors that cause myocardial damage unrelated to cardiopulmonary machine effects, so studies conducted on ischemia-reperfusion injury, damaging effect of surgical trauma, and other inflammatory factors which explain myocardial injury occurring in off-pump cardiac surgery. Protecting the myocardial metabolic status was the target of all researches. In another hand, postoperative complications significantly increase the financial burdens in cardiac surgery. This made the corrections of surgical techniques and follow-up methods another goal, by which we could reduce the complication rates to acceptable levels.

One of the most important points is myocardial protection during the pre- and postoperative periods, researches were concentrated on finding the methods that provide the best protection and avoid the harmful effects of cardiac surgery. Effect of cardiopulmonary bypass, ischemic reperfusion damage, direct trauma related to manipulation, coronary lesions and preload-afterload mismatch are factors affecting limits of myocardial damage. By modulation of techniques and judicious use of suitable drugs, we can attenuate myocardial damage. Using of some medications in the preoperative period found to be effective in reducing the harmful potency of open cardiac surgery, for example B Blockers found to be effective in reducing the possibility of dysrhythmias in the peri- and postoperative periods (22).

Many researches concentrated on the beneficial effects of preoperative statin use on reducing the postoperative complications and improvement of the outcome in open cardiac surgery (23,24,25). In another hand, statin use may reduce the biochemical parameters of systemic inflammation and myocardial damage (26,27). Extracorporeal circulation related oxidative damage may be the causative factor of LDL oxidation which may lead to aCL formation. This is possibly because of the structural similarity between cardiolipin and ox-LDL antigenic epitopes (28). Hojnik M et al documented the deposition of aCL in subendothelial cardiac tissues (29). In this study, we depend on the levels of anticardiolipin IgG and IgM antibodies as a mirror for the oxidative damage related to cardiopulmonary bypass machine.

There was no significant difference between preoperative and postoperative LDL cholesterol levels relating to statin usage (atorvastatin 40 mg/day). Despite that, anticardiolipin antibody levels showed significant decrease during preoperative, cardiopulmonary pump and 0. postoperative day periods in those patients using statins at least for 7 days prior to surgery. But after 24.th hour postoperative periods, the levels of anticardiolipin antibody found to be similar and not affected by statin usage. Ejection fraction measurements by echocardiography revealed significant fall in all patients in the 5.th postoperative day in comparison to preoperative measurements, but all other parameters found to be normal.

These findings support the beneficial effects of statin in the perioperative and early postoperative (first 24 hours) in open cardiac surgery.

Limitations of study: The main limitation of the study is the limited sample size. Another limitation is that the results reflect a single center experience. More extensive studies are needed to reach a definitive conclusion.

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