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Original Article / Özgün Makale

Does statin pre-treatment affect right atrial myocyte apoptosis in coronary artery bypass graft patients? an *in-vivo* pilot study

Koroner arter baypas greft hastalarında statin ön tedavisi sağ atriyal miyosit apoptozisini etkiler mi? In-vivo pilot çalışma

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Background: This study aims to investigate the possible protective effects of statin pretreatment against right atrial myocyte apoptosis in patients undergoing coronary artery bypass grafting.

Methods: Twenty-nine consecutive patients were included in the study. Group 1 patients (n=12; male: 83.3%) were initiated on atorvastatin 40 mg/day on the day of hospital admission and group 2 patients (n=17; male: 82.3%) did not receive statin therapy. Right atrial samples were taken before cardiopulmonary bypass and fixed in 10% neutral formalin. Immunoperoxidase staining and TUNEL method were performed to detect apoptotic cells. The immunostained active caspase-3 and proliferating cell nuclear antigen (PCNA) cells were counted using a light microscope.

Results: The mean apoptotic index was significantly lower in endocardial (p=0.04) and epicardial layers (p=0.01) of group 1 patients compared to those of group 2. Myocardial layer values were similar between the groups (p=0.35). The mean PCNA index in any layers was not significantly different between groups.

Conclusion: Statin pretreatment before CABG seems to diminish cardiac myocyte loss, providing an explanation for their beneficial effects seen after open heart surgery.

Keywords: Apoptosis; coronary artery bypass grafting; statin.

Amaç: Bu çalışmada koroner arter baypas greftleme yapılan hastalarda statin ön tedavisinin sağ atriyal miyositlerin apoptozisine karşı olası koruyucu etkileri araştırıldı.

Çalışma planı: Çalışmaya 29 ardışık hasta dahil edildi. Grup 1'deki hastalara (n=12; erkek: 83.3%) hastaneye yatış gününden itibaren atorvastatin 40 mg/gün tedavisi uygulandı, grup 2'deki hastalara (n=17; erkek: 82.3%) ise statin tedavisi uygulanmadı. Sağ atriyal örnekler kardiyopulmoner baypasa girilmeden önce alındı ve %10'luk nötral formalin ile fikse edildi. Apoptotik hücrelerin tespiti için immünoperoksidaz boyama ve TUNEL yöntemi kullanıldı. Immün boyamalı aktif kaspas-3 ve proliferatif hücre nükleer antijen (PCNA) hücrelerinin sayımı ışık mikroskopu kullanılarak yapıldı.

Bulgular: Grup 1'deki hastaların endokardiyal (p=0.04) ve epikardiyal (p=0.01) katmanlarındaki ortalama apoptotik indeks değerleri grup 2'dekilere kıyasla, anlamlı düzeyde düşük bulundu. Miyokardiyal katmanlardaki değerler arasında fark olmadığı görüldü (p=0.35). Katmanlar arasında ortalama PCNA indeksi açısından anlamlı fark yoktu.

Sonuç: Koroner arter baypas greftleme öncesi statin ön tedavisinin kardiyak miyosit kaybını azaltabileceği görünmekte olup, açık kalp cerrahisi sonrası yararlı etkilere işaret edebilir.

Anahtar sözcükler: Apoptoz; koroner arter baypas greftleme; statin.

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Apoptosis has increasingly become the object of intensive research and is considered to be the key mechanism involved in vital processes such as normal cell turnover, embryonic development, immune system maturation, hormone dependent atrophy, and tissue remodeling. Dysregulation of apoptosis plays a crucial role in the development of many disease processes where either too little or too much cell death constitutes the main pathogenetic mechanism.[1] In addition, cardiomyocyte apoptosis has been shown to be associated with the progress of cardiac failure, which is the natural result of an irreversible loss of functional cells. Olivetti et al.[2] showed that this scattered loss of cardiomyocytes induces compensatory alterations, including left ventricular hypertrophy and remodeling, and both of these have been the target of novel therapies within the last two decades. Further support was provided by another experimental model in which the inhibition of apoptosis attenuated the development of heart failure by preventing pressure overload.[3]

The perioperative use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor drugs (statins) in patients undergoing coronary artery bypass grafting (CABG) was extensively studied in the previous decade, and the latest guidelines strongly recommend the perioperative use of statins in this group of patients. A recent review also found that while statin pretreatment has no effect on perioperative mortality, it can reduce the risk of postoperative atrial fibrillation (AF) and shorten intensive care unit (ICU) and hospital stays.[4,5] In addition to a number of clinical and metabolic conditions, oxidative stress (OS) and ischemia-reperfusion (IR) injury were also found to be responsible for the development of AF, especially in cardiac surgical settings.[6,7] Several intrinsic and extrinsic stimuli, including specific receptor-ligand binding, hypoxia, ischemia, reperfusion, stretching, and oxidants, trigger apoptosis. Furthermore, a wide variety of intracellular execution cascades have demonstrated their dependence on mitochondrial apoptotic pathways.[8] In fact, the opening of the mitochondrial permeability transition pore, a well-known apoptotic pathway, is especially important as it serves a mechanism of cell death following myocardial IR,[9] another target for potential cardioprotective drugs. Although a recent in vitro human study[10] showed that pravastatin has cardioprotective properties via the inhibition of the mitochondrial permeability transition pathway, the effects of statins on cardiomyocyte apoptosis is still controversial since they have also been shown to stimulate this process.[11]

Indeed, Crow et al.[8] considered the amelioration of the disease process via the inhibition of apoptosis to be necessary in order to elucidate the possible relationship between it and other cardiac disease processes. We believe that the ultimate explanation of the therapeutic relationship between statin pretreatment and post-cardiac surgical AF deserves further exploration; therefore, this in vivo pilot study addressed the possible protective effect of statins against human right atrial myocyte apoptosis, which was previously proven to be associated with permanent AF.[12]

PATIENTS AND METHODS

A total of 66 consecutive patients underwent isolated CABG between April 20th and May 20th, 2012 at our facility. Ultimately 29 of these (25 males, 4 females; mean age 59.6±9.9 years; range 46 to 73 years) met our pre-accepted criteria and were included in this study, which received the approval of the institutional ethics committee. We also obtained the informed consent of each of the study participants. An additional characteristic of each of the patients was that they had multivessel coronary disease. Exclusion criteria included the following: severe left ventricular dysfunction [e.g., an ejection fraction (EF) of <35], previous cardiac surgery, previous use of statins and anti-arrhythmic drugs other than beta receptor antagonists, electrocardiography (ECG) findings of permanent or persistent AF along with cardiac rhythm or conduction disturbances, the presence of heart valve disease of any type and severity, a serum creatinine level of >2.0 mg/dL, moderate-to-advanced stage chronic obstructive pulmonary disease (COPD), and the presence of low serum hemoglobin.

The patients were divided into two groups according to whether or not they received atorvastatin pretreatment during their preoperative stay. The patients in group 1 (n=12; male: 83.3%) were initiated on atorvastatin 40 mg/day on the day of their hospital admission, and the treatment was continued until the day of operation. The patients in group 2 (n=17; male: 88.2%) did not receive any type of lipid-lowering therapy. The decision regarding whether or not an individual patient would be given the atorvastatin pretreatment was left to the discretion of the responsible surgeon.

All of the patients underwent elective surgery. Isolated CABG procedure was performed in a standardized fashion. The patients were premedicated with intravenous midazolam (0.08 mg/kg), and anesthesia was induced by thiopental (3 to 4 mg/kg) and fentanyl (2 to 6 g/kg). Invasive monitoring was carried out with a 20-gauge radial artery catheter, and a mixture

of 6% hydroxyethyl starch and saline was used for fluid management and maintenance. Right atrial samples were taken before systemic heparinization and the institution of cardiopulmonary bypass (CPB). Next, a midline sternotomy incision was made, and a pericardiotomy was performed. During this procedure, a purse string suture was sewn into the right atrial appendage using a double 3.0 polyprolene suture, with the cut ends being passed through a snare. Immediately after the snare was tightened, the right atrial appendage samples (2x2x0.5 cm^3 in size) were cut using Metzenbaum scissors and handled in a nontraumatic fashion. The harvesting of the left internal mammary artery (LIMA) along with the rest of the standard procedure was then carried out, and the right atrial appendage stump was used for venous cannulation.

The tissue samples were immediately fixed in 10% neutral formalin without any dissection and transported from the operating room to the laboratory on the same day as the surgery. The samples were then embedded in parafin wax and cut into sections measuring 4 μm in thickness. Afterwards, these were placed onto slides coated with poly-L-Lysine (PLL) (Sigma-Aldrich, St. Louis, MO, USA), deparaffinized in xylene, and rehydrated in graded alcohol.

The Histostain®-Plus Bulk Kit (Life Technologies Corporation, Carlsbad, CA, USA) was used for immunoperoxidase staining, and the immunohistochemistry procedure was used via a combination of microwave oven heating for antigen retrieval and the standard streptavidin-biotin-peroxidase method. Endogenous peroxidase activity was blocked by 3% H_2O_2. Each section was then incubated for 15 minutes at room temperature with the blocking solution, and the sections were incubated with proliferating cell nuclear antigen (PCNA) and a deoxyribonucleic acid (DNA) repair marker (dilution 1:200) or active (cleaved) caspase-3 antibodies (dilution 1:50) for one hour at room temperature. Following this, they were washed with phosphate buffered saline (PBS). Next, specific staining was performed with a biotinylated universal secondary antibody, a streptavidin-biotinylated horseradish peroxidase complex, and aminoethyl carbazole (AEC), which served as a chromogen, and the sections were then counterstained using Mayer's hematoxylen (Life Technologies Corporation, Carlsbad, CA, USA). For negative control, normal rabbit immunoglobulin G (IgG) was used. In addition, distilled water was used instead of the primary antibody.

The terminal transferase dUTP nick end labeling (TUNEL) method was used to detect apoptotic cells, and DNA fragmentation in situ was visualized with the use of the ApopTag® Plus Peroxidase In-Situ Apoptosis Detection Kit (EMD Millipore Corporation, Billerica, MA, USA). The deparaffinized tissue sections were incubated with proteinase K (20 μg/ml) and subjected to 3% hydrogen peroxide (H_2O_2) for endogenous peroxidase inhibition. They were then incubated with a 1x equilibration buffer at room temperature for 30 minutes, and the digoxigenin-labelled dNTP tail was incubated with terminal deoxynucleotidyl transferase (TdT) for one hour at 37 °C. Next, the tissue sections were washed in a stop/wash buffer for 10 minutes at room temperature. Afterwards, they were incubated with an anti-digoxigenin-peroxidase antibody at room temperature for 30 minutes and stained with diaminobenzidine (DAB) as a peroxidase substrate. Then they were evaluated using a light microscope after counterstaining with methyl green.

A morphometric analysis of the positive cells in the tissue stained by the TUNEL method was performed under high-power magnification (x400) in a blinded fashion. On each slide of the 29 samples, 15 fields were randomly selected, and the apoptotic index (AI) was calculated according to the following formula:

AI = [the number of apoptotic cells (AC)/AC + the number of intact cells (IC)] x 100.

The immunostained active caspase-3 and proliferating cell nuclear antigen (PCNA) cells were counted using a light microscope after calculating the PCNA index (PI) using the following formula:

PI= [the number of active caspase-3 or PCNA immunopositive cells/the number of total cells] x 100 PI.

Cell counts were performed using a x400 magnification in different fields, and at least 10 fields were evaluated per slide of the 29 patients. In addition, the counting of the cells was performed by two observers who were blinded to the treatment protocol.

Statistical analysis

All statistical analyses were performed using the SPSS version 16.0 software program (SPSS Inc,. Chicago, Illinois, USA). Continuous parameters were represented as mean ± standard deviation (SD), and categorical data was represented as number (percentages). In addition, proportions between two groups were compared using a chi-square test or Fisher's exact test. Furthermore, comparisons of the mean AI and PI values between the three atrial tissue layers were made using the Friedman test, and the Mann-Whitney U test was used to compare the mean index values and other non-parametric variables. An independent samples t-test was also used to compare

parametric variables, and a *p* value of <0.05 was considered to be statistically significant.

RESULTS

The two groups were similar in terms of baseline characteristics (Table 1). In group 1, the mean time from the initiation of statin pretreatment to the operation was 7.3±1.4 days (range 5-9 days), and no in-hospital mortality occurred. A reoperation for bleeding, which originated from the proximal site of the saphenous graft anastomosis, was required in one patient from group 1 (8.3%). Postoperative morbidities were infrequent in both groups (Table 2).

A morphometric analysis of the right atrial samples revealed that the mean AI was significantly lower in the myocardial layer compared with the other two layers (p=0.006). In addition, the mean AI was significantly lower in the endocardial (p=0.04) and epicardial layers (p=0.01) of group 1, but this difference was not observed in the myocardial layer (p=0.35). Nuclear immunostaining with the PCNA antibody was observed in some endocardial, myocardial, and epicardial cells. In all of the patients, the mean PI was significantly higher in the myocardial layer compared with the two other layers (p=0.003). Moreover, the mean PI in all of the layers did not differ significantly between the two groups. Caspase-3 immunostaining was also analyzed in the cardiomyocytes in the tissue samples taken from the right atrial samples, but this type of immunostaining, which was mostly limited to the cytoplasm, did not differ between the two groups (p=0.21) (Table 3).

DISCUSSION

We found that apoptosis was less prominent in the right atrial endocardium of the coronary artery patients who received short-course statin administration when compared to those who did not receive this pretreatment. Our findings indicates a possible mechanism for the preventive effect of statin therapy against AF in that it may enhance cellular viability and provide resistance against the adverse effects of cardiac surgery.

Although Pan et al.[13] showed that statin pretreatment reduced perioperative mortality in a previous retrospective study, a recent meta-analysis by Liakopoulos et al.[5] did not demonstrate any mortality effect. However, they did not the preventive effect of statin pretreatment against the development of postoperative AF. The results of this meta-analysis

Table 1. Baseline characteristics

Variable	Group 1 (n=12, 41.3%)			Group 2 (n=17, 58.6%)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age			60.4±9.6			59.1±10.5	0.80
Males	10	83.3		15	88.2		0.90
Body mass index (kg/m^2)			28.5±6.0			28.0±4.9	0.78
New York Heart Association class >II	6	35.3		7	15.9		0.16
Diabetes	5	41.7		5	29.4		0.69
Hypertension	8	66.7		8	41.7		0.29
Obstructive pulmonary disease	0	0		2	11.8		0.49
Total cholesterol			195.1±50.2			204.5±49.5	0.61
High-density lipoprotein cholesterol			43.7±10.0			43.1±9.4	0.86
Low-density lipoprotein cholesterol			109.3±46.2			120.4±41.8	0.50
Triglyceride level			222.2±48.4			208.0±42.1	0.40
Serum creatinine >1.5 mg/dl			0.9±0.2			0.9±0.2	0.94
Tobacco use	7	58.3		7	41.2		0.36
Beta receptor antagonists	11	91.7		15	88.2		0.95
Angiotensin-converting-enzyme inhibitors	2	16.7		3	17.6		0.94
Nitrates	5	41.7		8	47.1		0.77
Aspirin	1	8.3		5	29.4		0.35
Clopidrogel	1	8.3		0	0		0.41
Ejection fraction			58.1±10.0			59.4±8.8	0.81
Left ventricular end-diastolic diameter			4.7±0.4			4.9±0.7	0.73
Left atrial diameter			3.7±0.6			3.8±0.7	0.65

SD: Standard deviation.

Table 2. Postoperative variables

Variable	Group 1 (n=12, 41.3%)			Group 2 (n=17, 58.6%)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Number of diseased vessels			2.9±0.7			3.0±0.6	0.72
Cardiopulmonary bypass time			89.8±20.1			95.6±27.0	0.47
Need to inotropes	3	25.0		1	5.9		0.27
Intensive care unit stay (days)			1.8±0.8			1.6±0.8	0.47
Respiratory distress	0	0.0		1	5.9		0.98
Perioperative myocardial infarction	1	8.3		2	11.8		1.00
Atrial fibrillation	1	8.3		1	5.9		0.98

SD: Standard deviation.

were not conclusive for patients who underwent valve surgery because the majority of the studies included only CABG patients. Given the higher rates of AF following heart valve surgery, the routine use of statins has uniquely been recommended for CABG patients, demonstrating that an exact reduction in apoptotic rates by statin therapy seems to be worth pursuing because that may draw attention to the reproducibility of that effect in further studies designed for valve surgery patients.

Our study population was comprised of multivessel coronary artery patients with the right coronary artery necessarily being involved within its proximal segment. We excluded those patients with disease-free right coronary arteries since that would have been a confounding factor when we attempted to draw a conclusion based on the study findings. Also, because on-pump surgery has been thought to be associated with the development of postoperative AF via the induction of IR pathways,[14] we obtained the right atrial samples well before the institution of CPB. Furthermore, since the drugs used for anesthesia premedication and induction would as also have been confounding factors and blood leakage from the right atrial stump might have proven to be bothersome, the sample collection was also completed before the administration of systemic heparin and the harvesting of the internal mammary artery (IMA). Indeed, the samples were collected within approximately 30 minutes of the anesthesia induction in all of the patients. Other potential preoperative risk factors for the development of postoperative AF, such as poor left ventricular function, a history of AF, and the presence of systemic diseases, were taken into consideration when establishing the exclusion criteria to ensure control against patient selection bias. Moreover, the majority of the patients were receiving beta blockers upon admission to the hospital and that therapy was not discontinued until the day of the surgery. We believe that this approach ensured the creation of an isolated patient subgroup that clearly reflected the compared

Table 3. Mean apoptotic index, PCNA index, and caspase-3 activity values of the patients

	All patients	Group 1 (n=12, 41.3%)	Group 2 (n=17, 58.6%)	
	Mean±SD	Mean±SD	Mean±SD	*p*
Apoptotic index				
Endocardial layer	6.4±6.1	4.23±6.08	7.95±5.87	0.04
Myocardial layer	2.48±1.91	2.22±2.18	2.66±1.74	0.35
Epicardial layer	5.12±3.6	3.27±3.63	6.43±3.06	0.01
P value	0.006			
PCNA index (PI)				
Endocardial layer	0.4±1.4	0.01±0.001	0.7±1.8	0.44
Myocardial layer	14.5±9.2	12.10±8.80	15.60±9.60	0.28
Epicardial layer	1.50±3.7	0.41±1.39	2.36±4.71	0.34
P value	0.003			
Caspase-3 activity	2.00±1.24	1.62±1.37	2.27±1.11	0.21

PCNA: Proliferating cell nuclear antigen; SD: Standard deviation.

effects of the pretreatment. In addition, our findings may also serve as a reference point for the results of future studies that will be conducted within the context of AF.

One of our major findings was that the myocardial layer was observed to be better protected against the loss of myocytes than the endocardial and epicardial layers since the mean AI value was significantly lower in the microscopic fields examined within this layer. Given the subendocardial alignment of the atrial conduction fibers[15] and the important role that cellular mechanisms play in the development of AF, such findings support the concept that AF may be prevented by the inhibition of increased cellular automaticity through the preservation of myocyte survival.[16] However, further research involving human subjects is needed to verify this hypothesis. Additionally, the most prominent result of our study was that the mean AI was significantly lower in the patients who received statin pretreatment compared with those who did not. To overcome certain bias, for example the belief that long-term usage of lipid-lowering medications have an effect on the apoptotic process and cell survival, the patients who were taking lipid-lowering drugs before admission were not included in the study. Another focal point of this study concerned whether myocardial cells might be saved or whether the development of AF might be prevented on such short notice through the administration of any treatment. The results of the Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) randomized trial,[17] somewhat supported this theory by demonstrating the beneficial effects of short-term statin pretreatment, which was begun seven days before the surgery, on the development of postoperative AF. In addition, a number of experimental studies have demonstrated that apoptosis occurs within a relatively short time in cardiac tissue and its inhibition may even be achieved in hours.[18,19] Thus, the rationale of expecting an in vivo effect on apoptotic cell survival through the use of short-term statins may be advocated within this context.

The PCNA is a cofactor in DNA polymerase reactions and acts as a key component in DNA replication and repair processes. In addition, PCNA expression has been reported to be involved in the repair of DNA damage rather than acting as a marker of replication in cardiomyocytes.[20] Although the PI was significantly higher in the right atrial myocardial layers when compared with the endocardial and epicardial layers in this study, we found that the statin pretreatment had no effect on PCNA positivity. The most we can say is that short-course statin pretreatment seems to not have a prominent effect on PCNA positivity and that the known effects of long-term statin therapy on myocardial remodeling may be related to the inhibition of DNA damage. Thus, we believe that this topic warrants further investigation.

A number of studies have investigated the effect of certain conditions or drugs on right atrial myocyte apoptosis in patients undergoing open heart surgery.[12,21-25] Among these, an earlier study by Aimé-Sempé et al.[21] and a more recent one by Deniz et al.[12] demonstrated the presence of a positive relationship between right atrial myocyte apoptosis and chronic AF. However, Chang et al.[24] suggested that apoptosis was not more prominent in the right atrial tissue of patients with persistent AF when compared with those in sinus rhythm. However, the results of the latter study are a bit perplexing because the comparison group also had advanced heart valve disease and probably had a remodeled atrial architecture at the time of the operation. While each of the aforementioned studies made important conclusions regarding the issue of apoptosis and its implications in heart disease pathogenesis, it is still difficult to reach a common conclusion on the basis of the suggestions they made.

Limitations

The researchers did not intervene in an individual patient's preoperative medication regimen, leaving the decision in the hands of the responsible surgeon. Thus, we are aware that the nonrandomized design was the major drawback of this study. The postoperative outcomes were uneventful in a majority of the patients, and there was not an adequate number of events to make a conclusion regarding the clinical implications of the obtained results. Furthermore, the finite sample size was another major limitation that precluded the construction of an appropriate logistic regression model.

Conclusion

Statin pretreatment before CABG seems to provide protection against the loss of cardiac myocytes, which may affect postoperative outcomes and morbidity. Further studies with larger populations that randomize the patients into placebo-controlled arms, including those with valve disease, should provide more accurate information about the relationship we attempted to point out. Additionally, such studies might also provide more evidence concerning the pleiotropic effects of statins in humans and may extend their usage in the management of different patient groups.

Declaration of conflicting interests

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