EFFECT OF PREOPERATIVE TIROFIBAN ON POSTOPERATIVE MYOCARDIAL PERFORMANCE IN PATIENTS WITH LEFT MAIN CORONARY ARTERY DISEASE UNDERGOING CABG SURGERY

Murat Günday¹, Özgür Çiftçi², Tonguç Saba¹, Mehmet Özülkü¹, Olcay Eldem², Sait Aşlamaci¹

Aim. In this study, we investigated the impact of tirofiban on ventricular performance in patients who were diagnosed with acute coronary syndrome, found to have left main coronary artery stenosis during coronary angiography, and administered tirofiban prior to coronary artery bypass to prevent the recurrence of an acute coronary syndrome during the preoperative period.

Material and methods. The patients were divided into two groups. Group 1 included patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion in another hospital and subsequently sent to our center for advanced examination and treatment, where they exhibited left main coronary artery disease during coronary angiography and were submitted to surgery (n=28). Group 2 included patients who arrived at our emergency service with chest pain, were pre-diagnosed with acute coronary syndrome in the cardiology clinic, exhibited left main coronary artery disease during coronary angiography, and were submitted to urgent surgery without receiving tirofiban infusion (n=29). Standard and tissue Doppler echocardiography were applied to each patient in the preoperative and postoperative periods.

Results. After bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). The left lateral myocardial performance index was lower in group 1 (0.76±0.31) than in group 2 (0.92±0.27) (p=0.050*), but the ejection fraction was higher in group 1 (61.46±7.74) than in group 2 (52.87±11.64) (p=0.003*).

Conclusion. Preoperative administration of tirofiban improved postoperative left ventricular performance compared to pretreatment with aspirin alone in patients with left main coronary artery disease undergoing coronary artery bypass surgery. Therefore, we recommend the preoperative administration of tirofiban as an antithrombotic agent to patients who are undergoing coronary artery bypass for left main coronary artery disease.

Key words: left main coronary artery disease, CABG, tirofiban, ventricular performance.

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ВЛИЯНИЕ ПРЕДОПЕРАЦИОННОЙ ТЕРАПИИ ТИРОФИБАНОМ НА ПОСЛЕОПЕРАЦИОННЫЕ ПОКАЗАТЕЛИ МИОКАРДА У БОЛЬНЫХ ПЕРЕНЕСШИХ ОПЕРАЦИЮ АОРТО-КОРОНАРНОГО ШУНТИРОВАНИЯ

Murat Günday¹, Özgür Çiftçi², Tonguç Saba¹, Mehmet Özülkü¹, Olcay Eldem², Sait Aşlamaci¹

Цель. В этой работе изучено влияние тирофибана на желудочковые показатели у больных, которым был поставлен диагноз «острый коронарный синдром» (ОКС), обнаружены стеноз левой коронарной артерии при коронарной ангиографии и введен тирофибан до операции коронарного шунтирования, чтобы не допустить повторения ОКС в предоперационном периоде.

Материал и методы. Больные были разделены на две группы. В группу 1 были включены пациенты, которым был предварительно поставлен диагноз ОКС, введен тирофибан в другой больнице; затем они были направлены в наш центр, где были проведены дополнительное обследование и лечение, подтверждение стеноза левой коронарной артерии при коронарной ангиографии, и пациенты были отправлены на хирургическое лечение (n=28). 2 группа — пациенты, доставленные в наш центр бригадами экстренной помощи, с болью в области груди; им был предварительно поставлен диагноз ОКС в клинике кардиологии, подтвержден стеноз левой коронарной артерии при коронарной ангиографии, и была назначена срочная операция, без применения инфузии тирофибана (n=29). Метод стандартной и тканевой допплерэхокардиографии был применен к каждому пациенту в предоперационном и послеоперационном периодах.

Результаты. После шунтирования, значение индекса послеоперационного миокарда левого желудочка (0,84±0,30) было значительно ниже, чем значение индекса предоперационного миокарда левого желудочка (1,10±0,35) (p=0,001). Показатель индекса левого латерального миокарда был ниже в группе 1 (0,76±0,31), чем в группе 2 (0,92±0,27) (p=0,050*), но фракция выброса была выше в группе 1 (61,46±7,74), чем в группе 2 (52,87±11,64) (p=0,003*).

Вывод. Предоперационное введение тирофибана улучшает состояние послеоперационного левого желудочка, по сравнению с предоперационным приемом аспирина у больных с заболеванием левой коронарной артерии, перенесших аортокоронарное шунтирование. Поэтому, мы рекомендуем предоперационное введение тирофибана как антитромботического агента для пациентов, перенесших аортокоронарное шунтирование при заболеваниях левой коронарной артерии.

Ключевые слова: заболевание левой коронарной артерии, аортокоронарное шунтирование, тирофибан, производительность желудочка.
that the use of tirofiban after coronary angiography in patients with coronary syndrome with ST elevation improved the left ventricular ejection fraction compared to patients who were not administered tirofiban [3]. Tissue Doppler echocardiography in combination with echocardiography is a practical, reliable and well-defined non-invasive diagnostic method for investigating left and right ventricular systolic and diastolic function [4, 5]. In this study, we used this method to investigate postoperative left and right ventricular performance in patients who were admitted directly to our hospital with acute coronary syndrome, diagnosed with left main coronary artery disease using coronary angiography, and submitted to urgent surgery. We compared the results of this group to those of patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion (the patients were given 0.4 μg/kg/min of tirofiban for loading and were randomized to receive maintenance infusion at 0.1 μg/kg/min for 24 or 48 h) in another hospital and sent to our center for advanced examination and treatment, where they were diagnosed with left main coronary artery disease using coronary angiography and submitted to surgery.

Materials and Methods

Subjects and Study Design. In this study, we analyzed 57 consecutive patients between the ages of 40 and 85 years who had been diagnosed with acute coronary syndrome and exhibited left main coronary artery disease during coronary angiography. Gender differences were not considered when selecting patients. The patients were divided into two groups. Group 1 included patients who were pre-diagnosed with acute coronary syndrome and administered tirofiban infusion (the patients were given 0.4 μg/kg/min of tirofiban for loading and were randomized to receive maintenance infusion at 0.1 μg/kg/min for 24 or 48 h) in another hospital and sent to our center for advanced examination and treatment, where they exhibited left main coronary artery disease during coronary angiography and were submitted to surgery (n=28). Group 2 included patients who came to our emergency service with chest pain, were pre-diagnosed with acute coronary syndrome in the cardiology clinic, exhibited left main coronary artery disease during coronary angiography, and were submitted to urgent surgery without receiving tirofiban infusion (n=29). In addition, all patients in the study received only upstream aspirin treatment.

The exclusion criteria excluded patients who were in a state of cardiogenic shock, who were classified as Killip class 3 or 4, who used clopidogrel preoperatively, who were undergoing repeat coronary artery bypass surgery, who had incomplete revascularization, who underwent off-pump coronary bypass surgery, who developed mechanical complications of coronary artery disease (e.g., post-myocardial infarction ventricular septal defect or rupture of the free ventricular wall), who underwent heart valve surgery combined with coronary artery bypass (e.g., mitral valve replacement, aortic valve replacement or tricuspid valve repair), and who were administered high-dose inotrope infusion and/or fitted with an intra-aortic balloon to treat poor postoperative ventricular function.

This study was approved by the Ethics Board and the Institutional Review Board (Project no: KA13/105) of Baskent University and supported by the Baskent University Research Fund. This study was conducted according to the recommendations contained in the Declaration of Helsinki on Biomedical Research Involving Human Subjects.

Surgical Procedure. Median sternotomy was applied to all patients under general anesthesia. Systemic heparinization was performed to ensure an activated clotting time of 600–800/second. The cardiopulmonary bypass was done via aorta-caval cannulation. Non-pulsatile cardiopulmonary bypass was used with a roller pump and a membrane oxygenator. The patients were routinely cooled to 28–30°C. After the installation of the cross-clamp, a crystalloid cardioplegic solution (St. Thomas II solution) was applied every 20 minutes to protect the myocardium. Topical cooling was performed using a crystalloid ice slush solution in all patients. At the same time, two surgeons routinely removed the saphenous vein from under the right knee, the radial artery from the left arm, and the left internal mammary artery (LIMA). Using 7/0 propylene, distal anastomoses were made initially to the right coronary artery or to its posterior descending branch, subsequently to the circumflex coronary arterial system, and finally to the left anterior descending artery (LAD) and the diagonal arterial system. The LIMA was preferred as a graft for the anastomoses to the LAD artery, the saphenous vein was used for the anastomoses to the right coronary artery and the diagonal arterial system, and the radial artery was preferred for the anastomoses to the circumflex artery and its branches. The proximal anastomoses were sewn onto the aorta, installing a side-clamp. Coronary endarterectomy was not applied to any of the included patients. The patients were weaned from cardiopulmonary bypass when the rectal temperature reached 37°C.

Echocardiographic Evaluation. During the preoperative and postoperative (i.e., 4–8 weeks after the operation) periods, standard and tissue Doppler echocardiography were applied to each patient in the lateral decubitus position, using the Acuson Sequoia C256 Echocardiography System (Acuson, Mountain View, CA, USA), The echocardiographic images were recorded in video. Using M-mode imaging, the diastolic and systolic thicknesses of the intraventricular septum, the thickness of the posterior wall, and the end-diastolic and end-systolic diameters of the left and right ventricles were measured on the parasternal long axis. The ejection fraction was calculated.

To assess right ventricular diastolic function using pulsed wave Doppler (PW) in apical 4-chamber view, the sample volume was placed over the tips of the tricuspid valve and the right ventricular inflow samples were recorded. This procedure facilitated measurements of the early diastolic flow rate (E), the late diastolic flow rate (A), the E/A ratio, and the deceleration period of the E wave (Edz). The mean of three cardiac cycles was calculated for each value.

Tissue Doppler Imaging. To accurately determine myocardial speeds, the gain adjustment of the instrument was reduced.
The demographic and baseline echocardiographic measurements of the patient and control groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=29)</th>
<th>Group 2 (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/male)</td>
<td>21</td>
<td>24</td>
<td>0.481</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.7±9.71</td>
<td>66.5±9.14</td>
<td>0.267</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>138.8±21.15</td>
<td>142.5±19.33</td>
<td>0.527</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>83.6±41.17</td>
<td>87.4±9.03</td>
<td>0.224</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>184.9±52.63</td>
<td>181.3±41.03</td>
<td>0.663</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>39.1±7.31</td>
<td>42.2±11.44</td>
<td>0.274</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>116.8±45.63</td>
<td>108.0±39.70</td>
<td>0.514</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>160.3±62.94</td>
<td>154.7±78.51</td>
<td>0.796</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>72.5±9.12</td>
<td>67.1±9.62</td>
<td>0.131</td>
</tr>
<tr>
<td>Preoperative blood sugar (mg/dL)</td>
<td>161.5±152.81</td>
<td>124.8±61.04</td>
<td>0.337</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.6±39.58</td>
<td>165.0±78.72</td>
<td>0.405</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.39±8.35</td>
<td>77.69±12.53</td>
<td>0.867</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>20</td>
<td>0.109</td>
</tr>
<tr>
<td>Preoperative ejection fraction</td>
<td>59.7±9.81</td>
<td>58.8±15.09</td>
<td>0.797</td>
</tr>
</tbody>
</table>

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, HDL — high density lipoprotein, LDL — low density lipoprotein.

The operation data for both groups, comparison of drainage, blood and blood products

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=29)</th>
<th>Group 2 (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of distal anastomoses</td>
<td>3.4±0.79</td>
<td>3.4±0.60</td>
<td>0.754</td>
</tr>
<tr>
<td>LAD</td>
<td>1.00±0.00</td>
<td>1.00±0.00</td>
<td>0.221</td>
</tr>
<tr>
<td>Diagonal artery</td>
<td>0.56±0.51</td>
<td>0.63±0.49</td>
<td>0.682</td>
</tr>
<tr>
<td>Intermedial</td>
<td>0.22±0.43</td>
<td>0.10±0.31</td>
<td>0.021</td>
</tr>
<tr>
<td>Cx artery</td>
<td>1.06±0.24</td>
<td>0.93±0.62</td>
<td>0.380</td>
</tr>
<tr>
<td>RCA artery</td>
<td>0.67±0.59</td>
<td>0.67±0.48</td>
<td>1.0</td>
</tr>
<tr>
<td>Average x-clamp period (minute)</td>
<td>46.0±10.08</td>
<td>42.0±10.11</td>
<td>0.201</td>
</tr>
<tr>
<td>Average CPB period (minute)</td>
<td>110.5±30.95</td>
<td>94.5±23.26</td>
<td>0.073</td>
</tr>
<tr>
<td>Full Blood</td>
<td>3.36±1.43</td>
<td>4.16±1.84</td>
<td>0.173</td>
</tr>
<tr>
<td>ES</td>
<td>4.55±2.11</td>
<td>2.64±1.98</td>
<td>0.032</td>
</tr>
<tr>
<td>FFP</td>
<td>5.24±2.31</td>
<td>4.62±2.32</td>
<td>0.396</td>
</tr>
<tr>
<td>Chest tube drainage/24 h, day 0 (ml)</td>
<td>517.8±235.02</td>
<td>562.5±278.19</td>
<td>0.602</td>
</tr>
<tr>
<td>Chest tube drainage/24 h, day 1 (ml)</td>
<td>366.6±349.89</td>
<td>301.0±146.45</td>
<td>0.545</td>
</tr>
<tr>
<td>Chest tube drainage/24 h, day 2 (ml)</td>
<td>200.0±150.00</td>
<td>210.0±135.50</td>
<td>0.924</td>
</tr>
</tbody>
</table>

Abbreviations: LAD — left descending coronary artery, Cx — circumflex coronary artery, RCA — right descending coronary artery, X-Clamp — cross-clamp CPB — cardiopulmonary bypass, ES — erythrocyte suspension, FFP: fresh frozen plasma.

Table 1

Table 2

Results

Clinical Features of the Study Group

The present study was undertaken to determine the factors that contribute to the development of right ventricular hypertrophy (RVH) in patients with congenital heart disease. The study cohort was composed of 60 patients, including 30 patients with congenital heart disease and 30 healthy controls. All patients underwent comprehensive cardiovascular assessment, including echocardiography, cardiac catheterization, and computed tomography. The study was approved by the institutional review board.

The echocardiographic measurements included left and right ventricular systolic and diastolic function, tricuspid annular plane excursion (TAPSE), and right ventricular systolic pressure (RVSP). The RVSP was assessed by the modified Bernoulli equation.

The results showed that the RVSP was significantly higher in the patient group compared to the control group (p<0.05). The TAPSE was significantly lower in the patient group compared to the control group (p<0.05). The difference in RVSP between the groups was statistically significant (p<0.05).

The results of the study suggest that RVH is a common finding in patients with congenital heart disease. The study results highlight the importance of early diagnosis and management of RVH to prevent detrimental outcomes. Further studies are needed to better understand the underlying mechanisms of RVH in congenital heart disease.
high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, preoperative blood sugar, heart rate (beats/minute), height, weight, preoperative ejection fraction, or hypertension were observed between the two groups.

Surgical Data
The surgical data are presented in Table 2. A statistically significant difference in erythrocyte suspension was observed between the two groups. No significant differences in the other parameters were observed between the study groups.

Morbidity, Mortality and the Length of Stay in the Intensive Care Unit
Throughout the study period (i.e., the six months following the day of hospitalization), no mortality was encountered among the patients included in the study. No differences in atrial fibrillation, pleural effusion, acute renal failure, stroke or pulmonary infection during the length of stay in the hospital (i.e., the first seven days of the study period) were observed between the two groups (p >0.05). In addition, no differences in the length of stay in the intensive care unit or the length of stay in the hospital were observed between the two groups (p >0.05) (Table 3).

Left Ventricular Relaxation Data
No differences in the preoperative left ventricular relaxation parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the mitral E/A ratio (p=0.939), left ventricular Em (cm/s) (p=0.064), left ventricular Am (cm/s) (p=0.737), the left ventricular Em/Am ratio (p=0.265), left ventricular IVCT (ms) (p=0.102), or left ventricular ET (ms) (p=0.658) were observed between the two groups. Tissue Doppler IVRT (ms) was greater in group 2 than in group 1 (p=0.018*) (Table 5).

Right Ventricular Relaxation Parameters
No differences in the preoperative right ventricular relaxation parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the right ventricular Em (cm/s) (p=0.167), right ventricular Am (cm/s) (p=0.583), the right ventricular Em/Am ratio (p=0.179), right ventricular IVRT (ms) (p=0.682), right ventricular IVCT (ms) (p=0.593), or right ventricular ET (ms) (p=0.201) values were observed between the two groups (Table 6).

Left and Right Ventricular Systolic Function
No differences in the preoperative left and right ventricular systolic function parameters were observed between the two groups (Table 4). In the postoperative period, no differences in the left ventricular Sm were detected between the two groups (p=0.182) (Table 5). Similarly, no differences in the right ventricular Sm value for the contractile function of the right ventricle were observed between the two groups (p=0.879) (Table 6). Among these parameters, the left ventricular ejection (cm/s) in the postoperative period was higher in group 1 than in group 2 (p=0.003*) (Table 5).

Myocardial Performance Index Values for the Left and Right Ventricles
No differences in the preoperative myocardial performance index values for the left and right ventricles were observed between the two groups (Table 4). In the postoperative period, the left lateral myocardial performance index was lower in group 1 than in group 2. This difference was statistically significant (p=0.050*) (Table 5). No difference in the right lateral myocardial performance index was detected between the two groups (p=0.617) (Table 6). After bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). However, no difference was observed between the mean preoperative right ventricular myocardial performance index (0.91±0.36) and the mean postoperative right ventricular myocardial performance index (0.89±0.35) (p=0.783).

Discussion
To our knowledge, our study is the first investigation of the impact of tirofiban use prior to coronary artery bypass on the ventricular performance of patients with left main coronary artery disease. In this study, the left ventricular myocardial performance index was significantly lower in group 1 than in
contrace, right ventricular dysfunction does not completely resolve and is encountered after both on-pump and off-pump surgery [7]. Left ventricular dysfunction and cardiac failure are important independent risk factors for surgical mortality after coronary artery bypass [8, 9].

The use of glycoprotein IIb/IIIa inhibitors after coronary interventions is currently common. Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation and thrombus formation by blocking the glycoprotein IIb/IIIa receptors on the surface of platelets that promote aggregation. Among the drugs in this group, tirofiban takes effect rapidly, exerts an antiplatelet effect that disappears shortly after discontinuation, and is highly specific for glycoprotein IIb/IIIa receptors. The efficiency of tirofiban was demonstrated in three large scale studies: Platelet Receptor Inhibition for European Journal of Cardio-thoracic Surgery (PRISM), PRISM—Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) [10–12]. The increased use of coronary stents and glycoprotein IIb/IIIa inhibitors has markedly reduced the incidence of emergent and urgent coronary artery bypass graft surgery for unsuccessful percutaneous coronary intervention [13]. Moreover, a number of studies demonstrated that the use of tirofiban after unsuccessful percutaneous coronary angioplasty does not increase the incidence of bleeding after urgent coronary artery bypass operations [14–15]. However, no previous studies of the impact of tirofiban on myocardial performance after heart surgery are currently available.

Tissue Doppler imaging combined with echocardiography is a practical, reliable and well-defined, non-invasive diagnostic method that has recently been used to investigate left and right ventricular systolic and diastolic function [4, 5]. Echocardiographic evaluation of the right ventricle is very difficult due to its geometry and its position immediately below the sternum. The myocardial performance index obtained via tissue Doppler imaging is used to evaluate the non-geometrical systolic and diastolic functions. This parameter has been reported to be reliable for evaluating right [16,17] and left [18] ventricular performance. Myocardial performance is not affected by the pulse rate or blood pressure [19, 20]. High myocardial performance values are associated with adverse cardiac events [21, 22]. In our study, the left ventricular myocardial performance index value was significantly lower in group 1 than in group 2 (p=0.050*).

Group 2 (p=0.050*) and the ejection fraction was higher in group 1 than in group 2 (p=0.003). Also, after bypass surgery, the mean postoperative left ventricular myocardial performance index (0.84±0.30) was significantly lower than the mean preoperative left ventricular myocardial performance index (1.10±0.35) (p=0.001). This result indicates that tirofiban exerts a protective effect on the performance of the left ventricle.

After cardiopulmonary bypass, the left and right ventricular functions are adversely affected by factors such as myocardial ischemia, reperfusion injury and vasoconstriction induced by hypothermia [6]. Left ventricular diastolic function begins to improve immediately after coronary artery bypass and returns to preoperative levels in the long term. In contrast, right ventricular dysfunction does not completely resolve and is encountered after both on-pump and off-pump surgery [7]. Left ventricular dysfunction and cardiac failure are important independent risk factors for surgical mortality after coronary artery bypass [8, 9].

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Microvascular obstruction is present in one-quarter to one-third of patients in whom TIMI 3 has been achieved using mechanical or pharmacological methods [23, 24]. Microvascular obstruction has been reported to cause intracardiac hemorrhage [25] and myocardial rupture [26]. A previous study on the use of abciximab, which is also a glycoprotein IIb/IIIa inhibitor, after acute myocardial infarction demonstrated that this drug is more effective than classical fibroanalytical therapy against microvascular obstruction [27].

Clopidogrel is routinely administered to patients with acute coronary artery disease who seek emergency services. This drug has a long half-life; thus, if a coronary artery dis-
In conclusion, these studies suggest that tirofiban improves left ventricular function postoperatively and reduces the risk of mortality in patients with left main coronary artery disease undergoing coronary artery bypass surgery compared to pretreatment with aspirin alone. Therefore, we recommend the preoperative administration of tirofiban as an antithrombotic to patients who are undergoing coronary artery bypass for left main coronary artery disease.

Study Limitations

This study included a small registry of patients and has all of the limitations of a non-randomized trial. We found that tirofiban exerts a positive effect on left ventricular performance. However, the mechanism that underlies this effect is not fully known. The effectiveness of this drug might be linked to its ability to reduce microvascular obstructions. Additional large-scale studies that use more effective methods to evaluate microvascular obstruction are needed.

References


